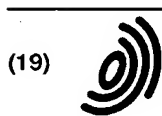


71



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 0 885 893 A1**

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
23.12.1998 Bulletin 1998/52

(51) Int. Cl.⁶: **C07D 307/92**, A61K 31/365,
C07D 307/33

(21) Application number: 97904575.4

(86) International application number:
PCT/JP97/00451

(22) Date of filing: 19.02.1997

(87) International publication number:
WO 97/30040 (21.08.1997 Gazette 1997/36)

(84) Designated Contracting States:
CH DE DK ES FR GB IT LI NL SE

(30) Priority: 19.02.1996 JP 31061/96
29.08.1996 JP 228005/96
18.12.1996 JP 338308/96

(71) Applicant:
MEIJI SEIKA KAISHA LTD.
Chuo-ku Tokyo (JP)

(72) Inventors:
• KURIHARA, Kenichi
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)
• SHINEI, Rie
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)
• TANABE, Kiyoshi
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)
• YAMAMOTO, Yasuo
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)

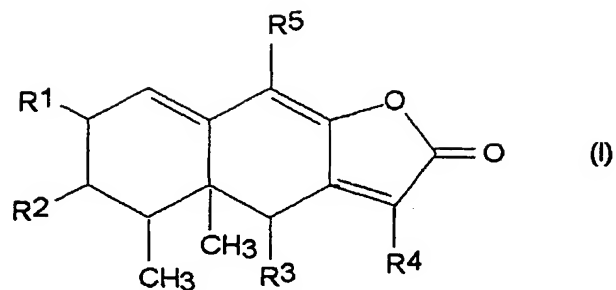
• AJITO, Kelichi
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)
• MIYAJIMA, Kaori
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)
• TABATA, Yuji
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)
• YASUDA, Shohei;
Waseda University;
Tokyo 169 (JP)
• TATSUTA, Kuniaki;
Waseda University;
Tokyo 169 (JP)
• OKONOGI, Tsuneo
Meiji Seika Kabushiki Kaisha
Yokohama-shi Kanagawa 222 (JP)

(74) Representative: Kyle, Diana
Elkington and Fife
Prospect House
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

(54) **NOVEL TETRAHYDRONAPHTHOFURANONE DERIVATIVES AND PROCESS FOR PRODUCING THE SAME**

(57) Compounds represented by the following formula (I) and pharmaceutically acceptable salts thereof are disclosed. The compounds have progesterone receptor binding inhibitory activity and, hence, can be used as therapeutic and prophylactic agents for progesterone-related diseases. Specifically, they are useful as abortifacients, oral contraceptive pills, carcinostatic agents for breast cancer and ovarian cancer, therapeutic agents for endometriosis, meningioma, and myeloma, and therapeutic and prophylactic agents for osteoporosis and climacteric disturbance.

EP 0 885 893 A1



wherein

R¹ and R² represent a hydroxyl group, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyloxy, alkoxyalkyloxy, cycloalkylcarbo-
nyloxy, alkoxy-carbonyloxy, aryloxy carbonyloxy, aralkylcarbonyloxy, aromatic acyloxy, heteroaromatic acyloxy, sat-
urated heterocyclic carbonyloxy, alkylsulfonyloxy, aromatic sulfonyloxy, alkylcarbamoxyloxy, aromatic carbamoxyloxy,
alkylcarbonylamino, or aromatic acylamino, provided that R¹ may further represent a hydrogen atom, alkyl, alkenyl,
or alkynyl; and R³, R⁴, and R⁵ each independently represent a hydrogen atom, alkyl or alkenyl.

Description

[BACKGROUND OF THE INVENTION]

5 Field of Invention

The present invention relates to compounds having progesterone receptor binding inhibitory activity and pharmaceutical compositions containing the same.

10 Background Art

In recent years, also in Japan, there is a tendency for the number of patients suffering from breast cancer to increase, and it is foreseen that the number of patients suffering from breast cancer would become largest among the malignant tumors in women in the 21st century. Ovariectomy has for the first time been used as endocrinotherapy for breast cancer. Thereafter, adrenalectomy and hypophysectomy have been reported to be useful as therapy for breast cancer in progress, and, since then, surgical endocrinotherapy has been mainly used and made progress. In the surgical endocrinotherapy, an organ involved in the secretion of estrogen is removed to regress estrogen dependent breast cancer. This, however, results in loss of not only estrogen but also life-sustaining hormones, including steroid hormones, posing many problems associated with the quality of life.

20 Non-steroidal anti-estrogen agents typified by Tamoxifen Citrate which appeared in the latter half of 1970s, by virtue of high effect against breast cancer and much lower side effect than conventional androgen and estrogen, have become extensively applied in clinical investigations and replaced the surgical endocrinotherapy used as main therapy for breast cancer up to that point.

More recently, agents having a new mechanism of action, such as medroxyprogesterone acetate (MPA) ("NYUGAN NO RINSHO", vol. 1, 201-213 (1986)), aromatase inhibitor, luteinizing hormone releasing hormone (LH-RH) agonist ("GAN TO KAGAKU RYOHO", 16, 2729 (1994)) have been developed, resulting in diversified endocrinotherapy for breast cancer.

30 On the other hand, the treatment of breast cancer with an antiprogestosterone agent based on progesterone receptor has been actively attempted particularly in recent years. For example, Mifepristone (RU38486) (FR2497807), Onapristone (ZK98299) (DE3321826) are under development.

Since, however, all of them have a steroidal skeleton, they have been pointed out to have side effect characteristic of steroid. Therefore, in order to overcome these problems, the appearance of an agent having progesterone receptor binding inhibitory activity without the steroid skeleton has been desired in the art.

35 The present inventors have previously succeeded in isolation of substance PF1092, having inhibitory activity against binding of progesterone to progesterone receptor, from a cultured mixture of a strain belonging to the genus *Penicillium* (Japanese Patent Application Nos. 20860/1995 and 17074/1996 and EP96100580.8, which are incorporated herein by reference).

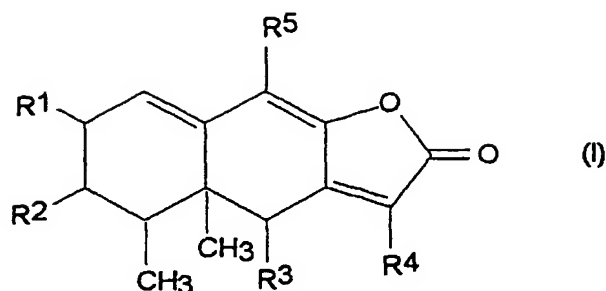
[SUMMARY OF THE INVENTION]

40 The present inventors have now succeeded in synthesis of various derivatives of substance PF1092 and confirmed that these derivative still have progesterone receptor binding inhibitory activity. The present invention is based on such novel finding.

45 Thus, according to one aspect of the present invention, there is provided a compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:

50

55



15 wherein

R¹ represents

a hydroxyl group,

optionally substituted C₁-C₁₀ alkyloxy,

20 optionally substituted C₂-C₁₀ alkenyloxy,

optionally substituted C₂-C₁₀ alkynyloxy,

C₃-C₆ cycloalkyloxy,

C₂-C₁₂ alkoxyalkyloxy,

five- or six-membered cycloalkyloxy containing one oxygen atom,

25 optionally substituted C₇-C₁₅ aralkyloxy,

optionally substituted C₂-C₁₁ alkylcarbonyloxy,

optionally substituted C₃-C₁₁ alkenylcarbonyloxy,

optionally substituted C₃-C₁₁ alkynylcarbonyloxy,

C₄-C₁₅ cycloalkylcarbonyloxy,

30 C₂-C₁₁ alkoxy carbonyloxy,

C₇-C₁₅ aryloxy carbonyloxy,

optionally substituted C₆-C₁₅ aralkylcarbonyloxy,

optionally substituted C₇-C₁₅ aromatic acyloxy,

35 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,

optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,

C₁-C₆ alkylsulfonyloxy,

optionally substituted C₆-C₁₂ aromatic sulfonyloxy,

40 C₂-C₇ alkylcarbonyloxy

optionally substituted C₇-C₁₂ aromatic carbonyloxy,

optionally substituted C₂-C₁₁ alkylcarbonylamino,

optionally substituted C₇-C₁₅ aromatic acylamino,

a hydrogen atom,

45 optionally substituted C₁-C₁₀ alkyl,

optionally substituted C₂-C₁₀ alkenyl, or

optionally substituted C₂-C₁₀ alkynyl;

R² represents

a hydroxyl group,

50 optionally substituted C₁-C₁₀ alkyloxy,

optionally substituted C₂-C₁₀ alkenyloxy,

optionally substituted C₂-C₁₀ alkynyloxy,

C₃-C₆ cycloalkyloxy,

C₂-C₁₂ alkoxyalkyloxy,

55 five- or six-membered cycloalkyloxy containing one oxygen atom,

optionally substituted C₇-C₁₅ aralkyloxy,

optionally substituted C₂-C₁₁ alkylcarbonyloxy,

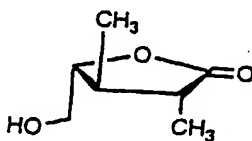
optionally substituted C₃-C₁₁ alkenylcarbonyloxy,

optionally substituted C₃-C₁₁ alkynylcarbonyloxy,
 C₄-C₁₅ cycloalkylcarbonyloxy,
 C₂-C₁₁ alkoxy carbonyloxy,
 C₇-C₁₅ aryloxy carbonyloxy,
 5 optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 optionally substituted C₇-C₁₅ aromatic acyloxy,
 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,
 optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from the
 10 group consisting of nitrogen, oxygen, and sulfur atoms,
 C₁-C₆ alkylsulfonyloxy,
 optionally substituted C₆-C₁₂ aromatic sulfonyloxy,
 C₂-C₇ alkylcarbamoxyloxy
 optionally substituted C₇-C₁₂ aromatic carbamoxyloxy,
 15 optionally substituted C₂-C₁₁ alkylcarbonylamino,
 optionally substituted C₇-C₁₅ aromatic acylamino;
 R³ represents
 a hydrogen atom
 optionally substituted C₁-C₁₀ alkyl, or
 20 optionally substituted C₂-C₁₀ alkenyl;
 R⁴ represents
 a hydrogen atom
 optionally substituted C₁-C₁₀ alkyl, or
 optionally substituted C₂-C₁₀ alkenyl; and
 25 R⁵ represents
 a hydrogen atom
 optionally substituted C₁-C₁₀ alkyl, or
 optionally substituted C₂-C₁₀ alkenyl,

30 provided that a compound wherein both R¹ and R² represent a hydroxyl group, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl, a compound wherein R¹ represents methylcarbonyloxy, and R² represents a hydroxyl group, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl, a compound wherein R¹ represents a hydroxyl group, R² represent methylcarbonyloxy, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl are excluded.

35 According to another aspect of the present invention, there is provided a process for producing a compound represented by the formula (I) according to claim 1, wherein R¹ and R² represent a hydroxyl group, R³ represents a hydrogen atom, R⁴ represents a hydrogen atom, optionally substituted C₁-C₁₀ alkyl, or C₂-C₁₀ alkenyl and R⁵ represents a hydrogen atom, said process comprising the steps of:

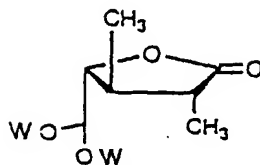
40 (a) oxidizing the following compound (11):



(1 1)

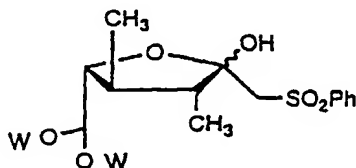
50 and then conducting acetal protection;

(b) reacting the resultant compound (12):



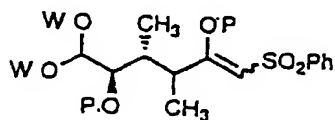
(1 2)

wherein W is a protective group of an acetal group, with benzenesulfonylmethyl in the presence of a base;
(c) protecting the resultant compound (13):



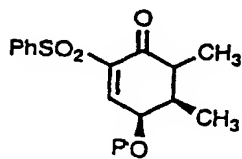
(1 3)

with a hydroxyl group and then conducting a ring-opening reaction in the presence of a base;
(d) subjecting the resultant compound (14):



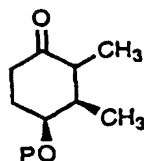
(1 4)

to a ring-closing reaction with a Lewis acid;
(e) reducing the resultant compound (15):



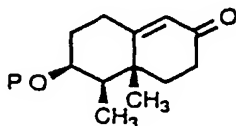
(1 5)

(f) subjecting the resultant compound (16):



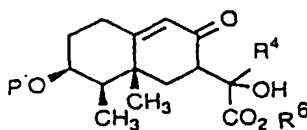
(1 6)

and 3-trimethylsilyl-3-buten-2-one to Michael addition and cyclocondensation in the presence of a base;
(g) condensing the resultant compound (17):



(1 7)

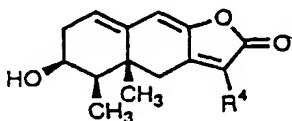
with α -keto ester by aldol condensation in the presence of a base and optionally a catalytic amount of zinc chloride;
(h) heating the resultant compound (18):



(1 8)

wherein R^4 is as defined above in connection with the formula (I) and R^6 is as defined above, under reflux in the presence of an acid catalyst;

(i) oxidizing the resultant compound (19):



(1 9)

[BRIEF DESCRIPTION OF THE DRAWINGS]

Fig. 1 is a graph showing infrared absorption spectrum of substance PF1092A in KBr tablet.
Fig. 2 is a graph showing 400 MHz ^1H NMR spectrum of substance PF1092A in CDCl_3 solution.
Fig. 3 is a graph showing 100 MHz ^{13}C NMR spectrum of substance PF1092A in CDCl_3 solution.
Fig. 4 is a graph showing infrared absorption spectrum of substance PF1092B in KBr tablet.
Fig. 5 is a graph showing 400 MHz ^1H NMR spectrum of substance PF1092B in CDCl_3 solution.
Fig. 6 is a graph showing 100 MHz ^{13}C NMR spectrum of substance PF1092B in CDCl_3 solution.
Fig. 7 is a graph showing infrared absorption spectrum of substance PF1092C in KBr tablet.

Fig. 8 is a graph showing 400 MHz ^1H NMR spectrum of substance PF1092C in CDCl_3 solution.

Fig. 9 is a graph showing 100 MHz ^{13}C NMR spectrum of substance PF1092C in CDCl_3 solution.

[Detailed Description of the Invention]

Definition

As used herein, the terms "alkyl," "alkenyl," and "alkynyl" as a group or a part of a group respectively mean straight or branched chain alkyl, alkenyl, and alkynyl. The term "halogen" used herein means a fluorine, chlorine, bromine, or iodine atom. The term "aralkyl" used herein means benzyl, phenylethyl (phenethyl), methylbenzyl, naphthyl or the like. The term "acyl" used herein means alkoxycarbonyl or arylcarbonyl. The term "aryl" preferably means phenyl, naphthyl, tolyl or the like.

Compounds represented by formula (I)

In the formula (I), the $\text{C}_1\text{-C}_{10}$ alkyloxy represented by R^1 and R^2 is preferably $\text{C}_1\text{-C}_6$ alkyloxy, more preferably $\text{C}_1\text{-C}_4$ alkyloxy. At least one hydrogen atom on the alkyloxy may be substituted by a substituent.

The $\text{C}_2\text{-C}_{10}$ alkenyloxy represented by R^1 and R^2 is preferably $\text{C}_2\text{-C}_6$ alkenyloxy, more preferably $\text{C}_2\text{-C}_4$ alkenyloxy. At least one hydrogen atom on the alkenyloxy may be substituted by a substituent.

The $\text{C}_2\text{-C}_{10}$ alkynyloxy represented by R^1 and R^2 is preferably $\text{C}_2\text{-C}_6$ alkynyloxy, more preferably $\text{C}_2\text{-C}_{10}$ alkynyloxy. At least one hydrogen atom on the alkynyloxy may be substituted by a substituent.

Examples of the $\text{C}_3\text{-C}_6$ cycloalkyloxy represented by R^1 and R^2 include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy.

The $\text{C}_2\text{-C}_{12}$ alkoxyalkyloxy represented by R^1 and R^2 is preferably $\text{C}_1\text{-C}_6$ alkoxy $\text{C}_1\text{-C}_6$ alkyloxy, more preferably $\text{C}_1\text{-C}_4$ alkoxy $\text{C}_1\text{-C}_4$ alkyloxy. Examples of the $\text{C}_7\text{-C}_{15}$ aralkyloxy represented by R^1 and R^2 include benzyloxy, phenylethyloxy, methylbenzyloxy, and naphthylmethyloxy.

The $\text{C}_2\text{-C}_{11}$ alkylcarbonyloxy represented by R^1 and R^2 is preferably $\text{C}_2\text{-C}_7$ alkylcarbonyloxy, more preferably $\text{C}_2\text{-C}_5$ alkylcarbonyloxy. At least one hydrogen atom on the alkylcarbonyloxy may be substituted by a substituent.

The five- or six-membered cycloalkyloxy containing one oxygen atom, represented by R^1 and R^2 , includes tetrahydrofuryloxy and tetrahydropyranyloxy.

The $\text{C}_3\text{-C}_{11}$ alkenylcarbonyloxy represented by R^1 and R^2 is preferably $\text{C}_3\text{-C}_7$ alkenylcarbonyloxy, more preferably $\text{C}_3\text{-C}_5$ alkenylcarbonyloxy. At least one hydrogen atom on the alkenylcarbonyloxy may be substituted by a substituent.

The $\text{C}_3\text{-C}_{11}$ alkynylcarbonyloxy represented by R^1 and R^2 is preferably $\text{C}_3\text{-C}_7$ alkynylcarbonyloxy, more preferably $\text{C}_3\text{-C}_5$ alkynylcarbonyloxy. At least one hydrogen atom on the alkynylcarbonyloxy may be substituted by a substituent.

The $\text{C}_4\text{-C}_{15}$ cycloalkylcarbonyloxy represented by R^1 and R^2 is preferably $\text{C}_4\text{-C}_8$ cycloalkylcarbonyloxy, and examples thereof include cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclopentylcarbonyloxy, and cyclohexylcarbonyloxy.

The $\text{C}_2\text{-C}_{11}$ alkoxy carbonyloxy represented by R^1 and R^2 is preferably $\text{C}_2\text{-C}_7$ alkoxy carbonyloxy, more preferably $\text{C}_2\text{-C}_5$ alkoxy carbonyloxy.

Examples of the $\text{C}_7\text{-C}_{15}$ aryloxy carbonyloxy represented by R^1 and R^2 include phenylcarbonyloxy, naphthylcarbonyloxy, and tricarboxyloxy.

Examples of the $\text{C}_8\text{-C}_{15}$ aralkylcarbonyloxy represented by R^1 and R^2 include benzylcarbonyloxy, phenylethylcarbonyloxy, methylbenzylcarbonyloxy, and naphthylmethylcarbonyloxy. At least one hydrogen atom on the aralkylcarbonyloxy may be substituted by a substituent.

Examples of the $\text{C}_7\text{-C}_{15}$ aromatic acyloxy represented by R^1 and R^2 include benzoyloxy, trioyloxy, cinnamoyloxy, and naphthoyloxy. At least one hydrogen atom on the aromatic acyloxy may be substituted by a substituent.

The $\text{C}_3\text{-C}_{15}$ heteroaromatic acyloxy, having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms, represented by R^1 and R^2 is preferably a five- or six-membered heteroaromatic acyloxy group containing one oxygen or sulfur atom, for example, furoyloxy, pyranilcarbonyloxy, or thenoyloxy, or a five- or six-membered heteroaromatic acyloxy group containing a nitrogen atom and a sulfur atom, for example, thiazolylcarbonyloxy. The heteroaromatic ring, together with other ring, for example, a benzene ring, may form a condensed ring, and examples thereof include benzothiophene. At least one hydrogen atom on the heteroaromatic acyloxy may be substituted by a substituent, and examples of the substituent include $\text{C}_1\text{-C}_6$ alkyl.

Examples of the $\text{C}_4\text{-C}_{12}$ saturated heterocyclic carbonyloxy, having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms, represented by R^1 and R^2 include tetrahydrofurylcarbonyloxy and tetrahydropyranylcarbonyloxy. At least one hydrogen atom on the saturated heterocyclic carbonyloxy may be substituted by a substituent.

The $\text{C}_1\text{-C}_6$ alkylsulfonyloxy represented by R^1 and R^2 is preferably $\text{C}_1\text{-C}_4$ alkylsulfonyloxy.

Examples of the C₆-C₁₂ aromatic sulfonyloxy represented by R¹ and R² include phenylsulfonyloxy. At least one hydrogen atom on the aromatic sulfonyloxy may be substituted by a substituent.

The C₂-C₇ alkylcarbamoyloxy represented by R¹ and R² is preferably C₂-C₅ alkylcarbamoyloxy.

Examples of the C₇-C₁₂ aromatic carbamoyloxy represented by R¹ and R² include phenylcarbamoyloxy. At least one hydrogen atom on the aromatic carbamoyloxy may be substituted by a substituent.

The C₁-C₁₀ alkyl represented by R¹ and R² is preferably C₁-C₆ alkyl, more preferably C₁-C₄ alkyl. At least one hydrogen atom on the alkyl may be substituted by a substituent.

The C₂-C₁₀ alkenyl represented by R¹ and R² is preferably C₂-C₆ alkenyl, more preferably C₂-C₄ alkenyl. At least one hydrogen atom on the alkenyl may be substituted by a substituent.

The C₂-C₁₀ alkynyl represented by R¹ and R² is preferably C₂-C₆ alkynyl, more preferably C₂-C₄ alkynyl. At least one hydrogen atom on the alkynyl may be substituted by a substituent.

In the formula (I), the C₁-C₁₀ alkyl represented by R³ is preferably C₁-C₆ alkyl, more preferably C₁-C₄ alkyl. At least one hydrogen atom on the alkyl may be substituted by a substituent.

The C₂-C₁₀ alkenyl represented by R³ is preferably C₂-C₆ alkenyl, more preferably C₂-C₄ alkenyl. At least one hydrogen atom on the alkenyl may be substituted by a substituent.

In the formula (I), the C₁-C₁₀ alkyl represented by R⁴ is preferably C₁-C₆ alkyl, more preferably C₁-C₄ alkyl. At least one hydrogen atom on the alkyl may be substituted by a substituent.

The C₂-C₁₀ alkenyl represented by R⁴ is preferably C₂-C₆ alkenyl, more preferably C₂-C₄ alkenyl. At least one hydrogen atom on the alkenyl may be substituted by a substituent.

In the formula (I), the C₁-C₁₀ alkyl represented by R⁵ is preferably C₁-C₆ alkyl, more preferably C₁-C₄ alkyl. At least one hydrogen atom on the alkyl may be substituted by a substituent.

The C₂-C₁₀ alkenyl represented by R⁵ is preferably C₂-C₆ alkenyl, more preferably C₂-C₄ alkenyl. At least one hydrogen atom on the alkenyl may be substituted by a substituent.

The compound according to the present invention are represented by the formula (I). However, a compound wherein both R¹ and R² represent a hydroxyl group, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl (sometimes referred to as "substance PF1092C"), a compound wherein R¹ represents methylcarbonyloxy, and R² represents a hydroxyl group, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl (sometimes referred to as "substance PF1092B"), a compound wherein R¹ represents a hydroxyl group, R² represents methylcarbonyloxy, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl (sometimes referred to as "substance PF1092A") are excluded from the scope of the present invention.

Among the compounds represented by the formula (I) according to the present invention, the following groups of compounds are preferred.

Specifically, a group of preferred compounds are those represented by the formula (I) wherein

- R¹ represents
 - a hydroxyl group,
 - C₁-C₁₀ alkyloxy,
 - C₃-C₆ cycloalkyloxy,
 - C₂-C₁₂ alkoxyalkyloxy,
 - optionally substituted C₇-C₁₅ aralkyloxy,
 - optionally substituted C₂-C₁₁ alkylcarbonyloxy,
 - C₄-C₁₅ cycloalkylcarbonyloxy,
 - C₂-C₁₁ alkoxycarbonyloxy,
 - C₇-C₁₅ aryloxy carbonyloxy,
 - optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 - optionally substituted C₇-C₁₅ aromatic acyloxy,
 - optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,
 - optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,
 - C₁-C₆ alkylsulfonyloxy,
 - C₂-C₇ alkylcarbamoyloxy
 - optionally substituted C₇-C₁₂ aromatic carbamoyloxy,
 - optionally substituted C₂-C₁₁ alkylcarbonylamino,
- a hydrogen atom, or
- optionally substituted C₁-C₁₀ alkyl;
- R² represents a hydroxyl group;
- R³ represents

a hydrogen atom or
optionally substituted C₁-C₁₀ alkyl;
R⁴ represents
a hydrogen atom or
optionally substituted C₁-C₁₀ alkyl; and
R⁵ represents
a hydrogen atom or
optionally substituted C₁-C₁₀ alkyl.

Another group of preferred compounds are those represented by the formula (I) wherein

R¹ represents a hydroxyl group;
R² represents
a hydroxyl group,
C₁-C₁₀ alkyloxy,
C₃-C₆ cycloalkyloxy,
C₂-C₁₂ alkoxyalkyloxy,
optionally substituted C₇-C₁₅ aralkyloxy,
optionally substituted C₂-C₁₁ alkylcarbonyloxy,
C₄-C₁₅ cycloalkylcarbonyloxy,
C₂-C₁₁ alkoxy carbonyloxy,
C₇-C₁₅ aryloxy carbonyloxy,
optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
optionally substituted C₇-C₁₅ aromatic acyloxy,
optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,
optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,
C₁-C₆ alkylsulfonyloxy,
C₂-C₇ alkylcarbamoxyloxy
optionally substituted C₇-C₁₂ aromatic carbamoxyloxy,
optionally substituted C₂-C₁₁ alkylcarbonylamino,
a hydrogen atom, or
optionally substituted C₁-C₁₀ alkyl;
R³ represents
a hydrogen atom or
optionally substituted C₁-C₁₀ alkyl;
R⁴ represents
a hydrogen atom or
optionally substituted C₁-C₁₀ alkyl; and
R⁵ represents
a hydrogen atom or
optionally substituted C₁-C₁₀ alkyl.

Still another group of preferred compounds are those represented by the formula (I) wherein

R¹ and R² each independently represent
a hydroxyl group;
C₁-C₁₀ alkyloxy,
C₃-C₆ cycloalkyloxy,
C₂-C₁₂ alkoxyalkyloxy,
optionally substituted C₇-C₁₅ aralkyloxy,
optionally substituted C₂-C₁₁ alkylcarbonyloxy,
C₄-C₁₅ cycloalkylcarbonyloxy,
C₂-C₁₁ alkoxy carbonyloxy,
C₇-C₁₅ aryloxy carbonyloxy,
optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
optionally substituted C₇-C₁₅ aromatic acyloxy,

optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,

optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,

C₁-C₆ alkylsulfonyloxy,

C₂-C₇ alkylcarbamoyloxy

optionally substituted C₇-C₁₂ aromatic carbamoyloxy,

optionally substituted C₂-C₁₁ alkylcarbonylamino,

a hydrogen atom, or

optionally substituted C₁-C₁₀ alkyl;

R³ represents

a hydrogen atom or

optionally substituted C₁-C₁₀ alkyl;

R⁴ represents

a hydrogen atom or

optionally substituted C₁-C₁₀ alkyl; and

R⁵ represents

a hydrogen atom or

optionally substituted C₁-C₁₀ alkyl.

A further group of preferred compounds are those prepared by the formula (I) wherein

R¹ represents a hydrogen atom;

R² represents

a hydroxyl group,

C₂-C₁₀ alkylcarbonyloxy,

C₃-C₁₀ alkenylcarbonyloxy,

optionally substituted C₂-C₁₀ alkylcarbonyloxy,

C₄-C₁₅ cycloalkylcarbonyloxy,

optionally substituted C₈-C₁₅ aralkylcarbonyloxy,

optionally substituted C₇-C₁₅ aromatic acyloxy, or

optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one nitrogen, oxygen, or sulfur atom;

R³ represents

a hydrogen atom

optionally substituted C₁-C₁₀ alkyl, or

optionally substituted C₂-C₁₀ alkenyl;

R⁴ represents

a hydrogen atom,

C₁-C₁₀ alkyl,

optionally substituted C₁-C₁₀ alkyl,

optionally substituted C₂-C₁₀ alkenyl; and

R⁵ represents

a hydrogen atom

optionally substituted C₁-C₁₀ alkyl, or

optionally substituted C₂-C₁₀ alkenyl.

A group of more preferred compounds represented by the formula (I) include:
compounds wherein

R² represents 2-tetrahydropyranyloxy, propionyloxy, isobutyryloxy, chloroacetyloxy, phenylacetyloxy, cyclopropylcarbonyloxy, cyclohexylcarbonyloxy, cinnamoyloxy, benzoyloxy, 4-nitrobenzoyloxy, 2-thenoyloxy, 2-furoyloxy, 1-benzothiophen-2-ylcarbonyloxy, 4-methyl-5-thiazolylcarbonyloxy, n-propylcarbamoyloxy, or acetylamino and

R¹ represents a hydroxyl group;

compounds wherein

R² represents methoxy, acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, 2-furoyloxy, ethoxycarbonyloxy, phenoxycarbonyloxy, methylsulfonyloxy, or acetylamino and

R¹ represents methoxy;

compounds wherein

EP 0 885 893 A1

R² represents acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy and

R¹ represents ethoxy;

compounds wherein

R² represents acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy and

R¹ represents n-propyloxy;

compounds wherein

R² represents a hydroxyl group, acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-furoyloxy, 2-thenoyloxy, or methoxymethyloxy and

R¹ represents propionyloxy;

compounds wherein

R² represents a hydroxyl group,

R¹ represents benzyloxy, cyclopropylcarbonyloxy, cyclohexylcarbonyloxy, benzoyloxy, 4-nitrobenzoyloxy, 2-thenoyloxy, 2-furoyloxy, methylcarbamoyloxy, or n-propylcarbamoyloxy;

compounds wherein

R² represents 2-furoyloxy and

R¹ represents acetyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy;

compounds wherein

R² represents propionyloxy and

R¹ represents acetyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy;

compounds wherein

R² represents benzoyloxy and

R¹ represents methoxymethyloxy or methoxyethoxymethyloxy;

compounds wherein

R² represents methoxymethyloxy and

R¹ represents benzoyloxy; and

compounds wherein R² represents n-propylcarbamoyloxy and

R¹ represents n-propylcarbamoyloxy;

compounds wherein

R² represents phenylcarbamoyloxy and

R¹ represents phenylcarbamoyloxy.

Further, according to a preferred embodiment of the present invention, groups of preferred compounds represented by the formula (I) include:

compounds wherein

R¹ represents a hydrogen atom,

R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy,

R³ represents a hydrogen atom,

R⁴ represents methyl, and

R⁵ represents a hydrogen atom;

compounds wherein

R¹ represents a hydrogen atom,

R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy,

R³ represents a hydrogen atom,

R⁴ represents methyl, and

R⁵ represents methyl;

compounds wherein

R¹ represents a hydrogen atom,

R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy,

R³ represents a hydrogen atom,

R⁴ represents ethyl, and

R⁵ represents a hydrogen atom;

compounds wherein

R¹ represents a hydrogen atom,

R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furo-

loxy, or 2-thenoyloxy,

R³ represents a hydrogen atom,

R⁴ represents a hydrogen atom, and

R⁵ represents a hydrogen atom;

5 compounds wherein

R¹ represents a hydrogen atom,

R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furo-

loxy, or 2-thenoyloxy,

R³ represents methyl,

10 R⁴ represents methyl, and

R⁵ represents a hydrogen atom; and

compounds wherein

R¹ represents methyl,

R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furo-

15 loxy, or 2-thenoyloxy,

R³ represents a hydrogen atom,

R⁴ represents methyl, and

R⁵ represents a hydrogen atom.

20 According to another embodiment of the present invention, the following group of compounds may be mentioned as a group of preferred compounds. Specifically, preferred are a group of compounds represented by the formula (I) wherein

R¹ and R² each independently represent

25 a hydroxyl group,

optionally substituted C₁-C₁₀ alkyloxy,

optionally substituted C₂-C₁₀ alkenyloxy,

optionally substituted C₂-C₁₀ alkynyloxy,

C₃-C₆ cycloalkyloxy,

30 C₂-C₁₂ alkoxyalkyloxy,

five- or six-membered cycloalkyloxy containig one oxygen atom,

optionally substituted C₇-C₁₅ aralkyloxy,

optionally substituted C₂-C₁₁ alkylcarbonyloxy,

optionally substituted C₃-C₁₁ alkenylcarbonyloxy,

35 optionally substituted C₃-C₁₁ alkynylcarbonyloxy,

C₄-C₁₅ cycloalkylcarbonyloxy,

C₂-C₁₁ alkoxy carbonyloxy,

C₇-C₁₅ aryloxy carbonyloxy,

optionally substituted C₈-C₁₅ aralkylcarbonyloxy,

40 optionally substituted C₇-C₁₅ aromatic acyloxy,

optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,

optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,

45 C₁-C₆ alkylsulfonyloxy,

optionally substituted C₆-C₁₂ aromatic sulfonyloxy,

C₂-C₇ alkylcarbamoxyloxy

optionally substituted C₇-C₁₂ aromatic carbamoxyloxy,

optionally substituted C₂-C₁₁ alkylcarbonylamino;

50 R³ represents a hydrogen atom;

R⁴ represents

a hydrogen atom or

C₁-C₁₀ alkyl; and

R⁵ represents a hydrogen atom.

55

Among the above groups of compounds, a group of more preferred compounds are those wherein

R¹ and R² each independently represent

a hydroxyl group,

C₁-C₆ alkoxy group,

C₂-C₁₂ alkoxyalkoxy which may be substituted by C₁-C₆ alkoxy group,

C₇-C₁₅ aralkyloxy,

5 C₂-C₇ alkylcarbonyloxy which may be substituted by a halogen,

C₄-C₁₅ cycloalkylcarbonyloxy,

C₂-C₇ alkoxy carbonyloxy,

C₇-C₁₅ aryloxy carbonyloxy,

C₈-C₁₅ aralkylcarbonyloxy,

10 C₇-C₁₅ arylcarbonyloxy which may be substituted by nitro,

five- or six-membered heteroaromatic acyloxy containing one oxygen or sulfur atom,

five- or six-membered heteroaromatic acyloxy, containing a nitrogen or sulfur atom, which may be substituted by

C₁-C₆ alkyl,

15 five- or six-membered saturated heterocyclic carbonyloxy having at least one hetero atom selected from nitrogen,

oxygen, and sulfur atoms,

C₁-C₆ alkylsulfonyloxy,

C₂-C₇ alkylcarbamoyloxy,

C₇-C₁₂ arylcarbamoyloxy,

C₂-C₇ alkylcarbonylamino:

20 R³ represents a hydrogen atom;

R⁴ represents C₁-C₆ alkyl; and

R⁵ represents a hydrogen atom.

25 Since the compounds represented by the formula (I) according to the present invention have several asymmetric carbons, various isomers attributable to these carbons are considered. The present invention embraces these individual isomers and mixtures thereof.

The compounds represented by the formula (I) may be present in the form of a salt. Examples of the salt include pharmacologically acceptable salts, and specific examples thereof include lithium, sodium, potassium, magnesium, and calcium salts; salts with ammonium and suitable non-toxic amines, for example, C₁-C₆ alkylamine (for example, triethylamine) salts, C₁-C₆ alkanolamine (for example, diethanolamine or triethanolamine) salts, procaine salts, cyclohexylamine (for example, dicyclohexylamine) salts, benzylamine (for example, N-methylbenzylamine, N-ethylbenzylamine, N-benzyl-β-phenethylamine, N,N-dibenzylethylenediamine, or dibenzylamine) salts, and heterocyclic amines (for example, morpholine or N-ethylpyridine) salts; salts of hydrohalogenic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid and hydroiodic acid; inorganic acid salts such as sulfate, nitrate, phosphate, perchlorate and carbonate; salts of carboxylic acids such as acetic acid, trichloroacetic acid, trifluoroacetic acid, hydroxyacetic acid, lactic acid, citric acid, tartaric acid, oxalic acid, benzoic acid, mandelic acid, butyric acid, maleic acid, propionic acid, formic acid and malic acid; salts of amino acids such as arginic acid, aspartic acid and glutamic acid; and salts of organic acids such as methanesulfonic acid and p-toluenesulfonic acid.

40 Use of compounds represented by formula (I)/pharmaceutical compositions

The compounds, represented by the formula (I), according to the present invention have progesterone receptor binding inhibitory activity and, hence, can be used as therapeutic and prophylactic agents for progesterone-related diseases. The progesterone receptor has been reported to be expressed in breast, uterus, ovary, bone, central nerve and the like. Therefore, the compounds represented by the formula (I) are useful as therapeutic and prophylactic agents for progesterone-related diseases in these organs. More specifically, they are useful as abortifacients, oral contraceptive pills, carcinostatic agents for breast cancer and ovarian cancer, therapeutic agents for endometriosis, meningioma, and myeloma, and therapeutic and prophylactic agents for osteoporosis and climacteric disturbance. Especially, the compounds represented by the formula (I) according to the present invention have no steroid skeleton and, hence, are considered to be advantageously free from side effect inherent in steroid such as found in conventional progesterone receptor binding inhibitors having a steroid skeleton.

A pharmaceutical composition comprising as an active ingredient a compound of the present invention can be administered either orally or parenterally (e.g., intravenous injection, intramuscular injection, subcutaneous administration, rectal administration, percutaneous administration) to humans or animals other than humans.

55 The pharmaceutical composition comprising as an active ingredient a compound of the present invention may be made into a preparation suitable for an administration route to be adopted. Specifically, it may be made into any of the following preparations: an injection for intravenous or intramuscular injection; a capsule, a tablet, a granule, a powder, a pill, fine subitlaes, or a troche for oral administration; a preparation for rectal administration; an oleaginous supposi-

tory; and an aqueous suppository. The above-described various preparations can be prepared by a conventional method using an excipient, a filler, a binder, a wetting agent, a disintegrating agent, a surface active agent, a lubricant, a dispersing agent, a buffer, a preservative, a solubilizer, an antiseptic, a flavor, a soothing agent, a stabilizer and the like. Examples of the above additives which are nontoxic and employable in the preparations include milk sugar, fruit sugar, grape sugar, starch, gelatin, magnesium carbonate, synthetic magnesium silicate, talc, magnesium stearate, methyl cellulose, carboxymethyl cellulose or a salt thereof, gum arabic, polyethylene glycol, syrup, vaseline, glycerin, ethanol, propylene glycol, citric acid, sodium chloride, sodium sulfite and sodium phosphate.

The dosage of the compound of the present invention is properly determined in consideration of the symptom and the age and sex of a patient for each case. However, for the treatment of the above diseases, in particular, as a contraceptive pill or an carcinostatic agent for breast cancer or ovarian cancer, in case of intravenous injection, 0.01 mg/kg to 1000 mg/kg, preferably 0.1 mg/kg to 100 mg/kg of the compound is generally administered per day for adult human, desirably at one time or several times. In case of intramuscular injection, 0.01 mg/kg to 1000 mg/kg, preferably 0.1 mg/kg to 100 mg/kg of the compound is generally administered per day for adult human, desirably at one time or several times. In case of oral administration, 0.5 mg/kg to 2000 mg/kg, preferably 1 mg/kg to 1000 mg/kg of the compound is generally administered per day for adult human, desirably at one time or several times.

Preparation of compound represented by formula (I)

Preferably, the compounds represented by the formula (I) according to the present invention can be prepared by the following processes.

The compound represented by the formula (I) according to the present invention can be prepared by providing substance PF1092C as a starting compound and modifying the starting compound.

(a) Acylation of hydroxyl group at 6- and 7-positions

Substance PF1092C has a free secondary hydroxyl group at its 6- and 7-positions. One of them is a hydroxyl group at the position of allyl. Therefore, a substituent may be selectively introduced by taking advantage of a difference in reactivity.

Specifically, substance PF1092C may be reacted with a reagent capable of acylating a hydroxyl group, such as an acid halide or an acid anhydride, in the presence of an equivalent or excess amount of a base to acylate the hydroxyl group at the 6- and 7-positions. Either or both of the hydroxyl groups may be selectively acylated by selection of the reagent, the amount of the reagent added, the reaction temperature, and the reaction time.

Selective introduction of an acyl group into the hydroxyl group at the 7-position may be carried out by reacting substance PF1092C with one to three equivalents of an acylating agent in a solvent inert to the reaction (for example, methylene chloride, chloroform, 1,2-dichloroethane, benzene, or toluene) in the presence of one to three equivalents of a suitably bulky organic base (for example, diisopropylethylamine, isopropylcyclohexylamine or the like with one to three equivalents of diisopropylethylamine being preferred) at 20 to 30°C for 1 to 24 hr.

Selective introduction of an acyl group into the hydroxyl group at the 6-position may be carried out by any of the following two methods.

The first method is to react substance PF1092C with one to three equivalents of an acylating agent $R^{1*}COX$, wherein R^{1*} and X are as defined above, in a solvent inert to the reaction (for example, methylene chloride, chloroform, 1,2-dichloroethane, benzene, or toluene) in the presence of 1 to 1.5 equivalents of an organic base (for example, 4-dimethylaminopyridine, lutidine, or collidine with 1 to 1.5 equivalents of 4-dimethylaminopyridine being preferred) at 20 to 30°C for 1 to 24 hr.

The second method is a method, utilizing a silyl protective group, wherein after protection of the hydroxyl group at the 7-position with a silyl group, the hydroxyl group at the 6-position is acylated and, in the final stage, the protective group is removed. More specifically, substance PF1092C is reacted with an equivalent or excess amount of a silylating agent in a solvent (for example, dimethylformamide, acetonitrile, methylene chloride, chloroform, or THF) in the presence of a base (for example, imidazole, pyridine, 4-dimethylaminopyridine, lutidine, collidineimidazole with 2 equivalents or excess amount of imidazole being preferred) at 0 to 80°C for 1 to 24 hr. The silylating agent is not particularly limited, and silylating agents usable herein include, for example, those wherein the silyl group is t-butyldimethylsilyl, isopropyltrimethylsilyl, or ethyldimethylsilyl. Silylating agents wherein the silyl group is t-butyldimethylsilyl (TBDMS) include, besides TBDMSCl, TBDMSOCl, TBDMSO₂CF₃, and TBDMSCN. Preferably, TBDMSCl is used in an equivalent or excess amount. The resultant substance, of which the hydroxyl group at the 7-position has been protected with a silyl group, is then reacted with an equivalent or excess amount of an acylating agent in a solvent (for example, methylene chloride, chloroform, 1,2-dichloroethane, benzene, or toluene) in the presence of a base (for example, an organic base, such as 4-dimethylaminopyridine, pyridine, lutidine, collidine, triethylamine, or diisopropylethylamine) at 0 to 100°C for 1 hr to 2 days, thereby acylating the hydroxyl group at the 6-position. Thereafter, the silyl protective group

is removed to prepare a compound with the hydroxyl group at the 6-position being acylated. The removal of the protective group may be carried out by reacting the compound having the protective group with an equivalent or excess amount of a fluoride reagent, such as tetrabutylammonium fluoride (TBAF), hydrogen fluoride-pyridine complex or cesium fluoride, acetic acid, trifluoroacetic acid, hydrochloric acid or the like in a suitable solvent (THF, methylene chloride, acetonitrile or the like) at 20 to 100°C for 30 min to 5 hr. The use of an equivalent or excess amount of TBAF or hydrogen fluoride-pyridine complex is preferred.

Further, an acyl group may be introduced into the two hydroxyl groups respectively at the 6- and 7-positions by the following method. Specifically, substance PF1092C may be reacted with 4 to 5 equivalents of an acylating agent or an acid anhydride in a solvent (for example, methylene chloride, chloroform, 1,2-dichloroethane, benzene, or toluene) in the presence of a base (for example, an organic base, such as 4-dimethylaminopyridine, pyridine, diisopropylethylamine, lutidine, or collidine with 5 to 6 equivalents of 4-dimethylaminopyridine or 5 equivalents or excess amount of pyridine being preferred) at 20 to 30°C for 1 to 24 hr.

Furthermore, it is also possible to simultaneously synthesize, as a mixture, a compound with both the hydroxyl groups at the 6- and 7-positions being acylated, a compound with only the hydroxyl group at the 6-position being acylated, and a compound with only the hydroxyl group at the 7-position being acylated. Specifically, substance PF1092C is reacted with a large excess of an acylating agent or an acid anhydride in a solvent (for example, methylene chloride, chloroform, 1,2-dichloroethane, benzene, or toluene) in the presence of a suitably bulky organic base (with 2 to 10 equivalents of diisopropylethylamine being preferred) at 20 to 30°C for 5 to 24 hr. Thereafter, the three compounds may be separated from one another by suitable separating means (for example, silica gel column chromatography).

For the compound, with only the hydroxyl group at the 6- or 7-position acylated, prepared by the above method, the remaining hydroxyl group may further be modified. Further, the compounds represented by the formula (I) may be prepared by alkoxyalkylation, alkylation, carbamoylation, sulfonylation, or modification with acetal, as described in this specification.

(b) Carbamoylation of hydroxyl groups at 6- and 7-positions

The hydroxyl groups respectively at the 6- and 7-positions of substance PF1092C may be carbamoylated as follows.

Specifically, substance PF1092C may be reacted with an equivalent or excess amount of an isocyanate in a solvent (for example, DMF, methylene chloride, chloroform, benzene, or toluene) in the presence of a base (for example, an organic base, such as 4-dimethylaminopyridine, pyridine, lutidine, collidine, triethylamine, or diisopropylethylamine with a catalytic amount of 4-dimethylaminopyridine being preferred) at 25 to 120°C for 1 to 24 hr. Thus, three compounds, i.e., a compound with both the hydroxyl groups at the 6- and 7-positions being carbamoylated, a compound with only the hydroxyl group at the 6-position being carbamoylated, and a compound with only the hydroxyl group at the 7-position being carbamoylated, are obtained as a mixture. Thereafter, the three compounds may be separated from one another by suitable separating means (for example, silica gel chromatography).

Alternatively, after protection of the hydroxyl group at the 7-position with a silyl group by the above method, the hydroxyl group at the 6-position may be carbamoylated followed by removal of the protective group to prepare a compound with the hydroxyl group at the 6-position being selectively carbamoylated.

Furthermore, for the compound, with only the hydroxyl group at the 6- or 7-position acylated, prepared by the above method, the remaining hydroxyl group may be further modified. Furthermore, the compounds represented by the formula (I) may be prepared by alkoxyalkylation, alkylation, carbamoylation, sulfonylation, or modification with acetal, as described in this specification.

(c) Alkyloxylation or alkoxyalkyloxylation of hydroxyl group at 6- and 7-positions

The hydroxyl groups respectively at the 6- and 7-positions of substance PF1092C may be alkyloxyated or alkoxyalkyloxyated as follows.

Specifically, the alkyloxylation may be carried out by reacting substance PF1092C with R^3-X , wherein R^3 represents optionally substituted C_1-C_{10} alkyl or optionally substituted C_7-C_{15} aralkyl and X represents a halogen atom, in a solvent (for example, toluene, DMF, methylene chloride, chloroform, or benzene) in the presence of a base (for example, a metal hydride such as sodium hydride or potassium hydride) at a temperature of -40 to 40°C for 5 min to 2 days.

On the other hand, the alkoxyalkyloxylation may be carried out by reacting substance PF1092C with R^4-X , wherein R^4 represents optionally substituted C_2-C_{12} alkoxyalkyl and X represents a halogen atom, in a solvent (for example, methylene chloride, chloroform, benzene, or toluene) in the presence of a base (for example, an organic base such as pyridine, lutidine, collidine, triethylamine, or diisopropylethylamine) at a temperature of 20 to 100°C for 10 to 24 hr.

As a result of the above reaction, a compound with the hydroxyl group at 6- or 7-position being alkyloxyated or alkoxyalkyloxyated can be obtained.

For the compound, with only the hydroxyl group at the 6- or 7-position alkoxyolated or alkoxyalkoxyolated, prepared by the above method, the remaining hydroxyl group may be further modified. Further, the compounds represented by the formula (I) may be prepared by alkoxyalkylation, alkylation, carbamoylation, sulfonylation, or modification with acetal, as described in this specification.

(d) Modification with acetal

Modification of substance PF1092C with acetal may be carried out by reacting substance PF1092C with an equivalent or excess amount of a dihydro ether, such as dihydropyran, dihydrofuran, or ethyl vinyl ether, in a solvent (for example, toluene, benzene, methylene chloride, or chloroform) in the presence of an acid (for example, p-toluenesulfonic acid, or pyridinium p-toluenesulfonic acid preferably in an amount ranging from a catalytic amount to 3 equivalents) at 20 to 100°C for 10 min to 3 hr.

(e) Introduction of substituent having α configuration into 7-position

Although the hydroxyl group at the 7-position of substance PF1092C is of β configuration, a substituent having α configuration can be stereoselectively introduced into the 7-position by the following method.

Specifically, substance PF1092C may be reacted with a sulfonyl halide in the presence of an equivalent or excess amount of a base and, immediately after that, reacted with a nucleophilic reagent, such as water, alcohol or potassium acetate, to give a 7 α -o-substituted derivative wherein the 7-position has been subjected to Walden inversion.

More specifically, substance PF1092C is reacted with a sulfonyl halide in a solvent (for example, methylene chloride, chloroform, benzene, or toluene with methylene chloride being preferred) in the presence of a base (for example, an organic base, such as diisopropylethylamine, pyridine, lutidine, collidine, triethylamine, or 4-dimethylaminopyridine, preferably 1 to 3 equivalents of diisopropylethylamine) at -30 to 10°C for 5 min to one hr, followed by nucleophilic substitution. Sulfonylating agents usable herein include, besides methanesulfonyl chloride, p-toluenesulfonyl chloride and benzy sulfonyl chloride. In many cases, however, use of 1 to 2 equivalents of methanesulfonyl chloride offers good results. Nucleophilic reagents usable herein include water, alcohols, such as methanol, ethanol, and propanol, and metal salts of aliphatic carboxylic acids, such as potassium acetate, sodium acetate, potassium propionate, and sodium propionate. When the nucleophilic reagent is water or an alcohol, the reagent is used in an amount of 3 to 10 equivalents. Solvents usable in this reaction include methylene chloride, chloroform, and acetonitrile with methylene chloride being preferred. The reaction may be carried out at -30 to 10°C for 30 min to 5 hr. On the other hand, when the nucleophilic reagent is a metal salt of an aliphatic carboxylic acid, use of the reagent in an amount of 1 to 5 equivalents offers good results. Further, addition of a catalytic amount of a crown ether, such as 18-crown-6, accelerates the reaction. Solvents usable in this reaction include acetonitrile, chloroform, and methylene chloride with acetonitrile being preferred. The reaction may be carried out at 0 to 30°C for 30 min to 6 hr.

For the compound, with only the hydroxyl group at the 7-position being substituted, prepared by the above method, the remaining hydroxyl group may be further modified. Further, the compounds represented by the formula (I) may be prepared by alkoxyalkylation, alkylation, carbamoylation, sulfonylation, or modification with acetal, as described in this specification.

(f) Introduction of amino group into 6- or 7 position

An oxazoline ring may be constructed at the 6- or 7 - position of substance PF1092C followed by a ring-opening reaction to introduce an amino group into the 6- or 7-position.

Substance PF1092C is reacted with a nitrile in the presence of an excess amount of 2-acetoxyisobutryl bromide to give an oxazoline derivative with a nitrogen atom introduced at the 6- or 7-position in β configuration. The oxazoline derivative is then reacted with a nucleophilic reagent, such as water or an alcohol, in the presence of a suitable acid catalyst to give a novel compound with the 6- or 7-position being acylaminated. In the formation of the oxazoline ring, the amount of 2-acetoxyisobutryl bromide used is preferably an equivalent or excess amount. A nitrile corresponding to an acylamino group to be introduced, for example, acetonitrile, propionitrile, or benzonitrile, is used as a solvent in the reaction. The reaction may be carried out at -40 to 50°C for 10 min to 24 hr. In the subsequent ring-opening reaction, besides water, an alcohol, such as methanol or ethanol, may be used as the nucleophilic agent. Use of 0.1 to several equivalents of an organic acid, such as p-toluenesulfonic acid or trifluoromethanesulfonic acid, as the acid catalyst is preferred. When the nucleophilic reagent is water, use of an excess amount of an organic base, such as pyridine, is preferred from the viewpoint of preventing the system from becoming acidic. The reaction may be carried out at -20 to 120°C for 1 to 5 hr.

EP 0 885 893 A1

(g) Total synthesis of compounds represented by formula (I) (part 1)

According to another embodiment of the present invention, total synthesis of substance PF1092C as described in the following scheme has been established, permitting total synthesis of the compounds represented by the formula (I).

5 The synthesis will be described in the order of description of scheme.

10

15

20

25

30

35

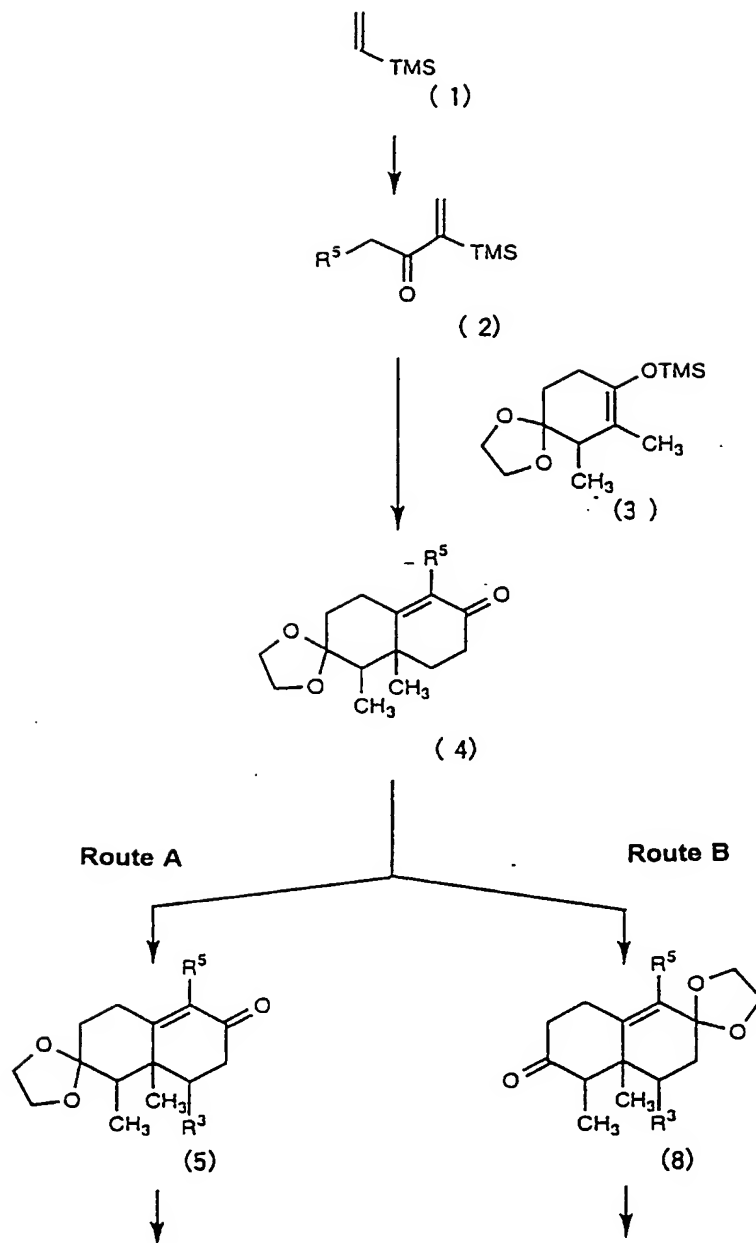
40

45

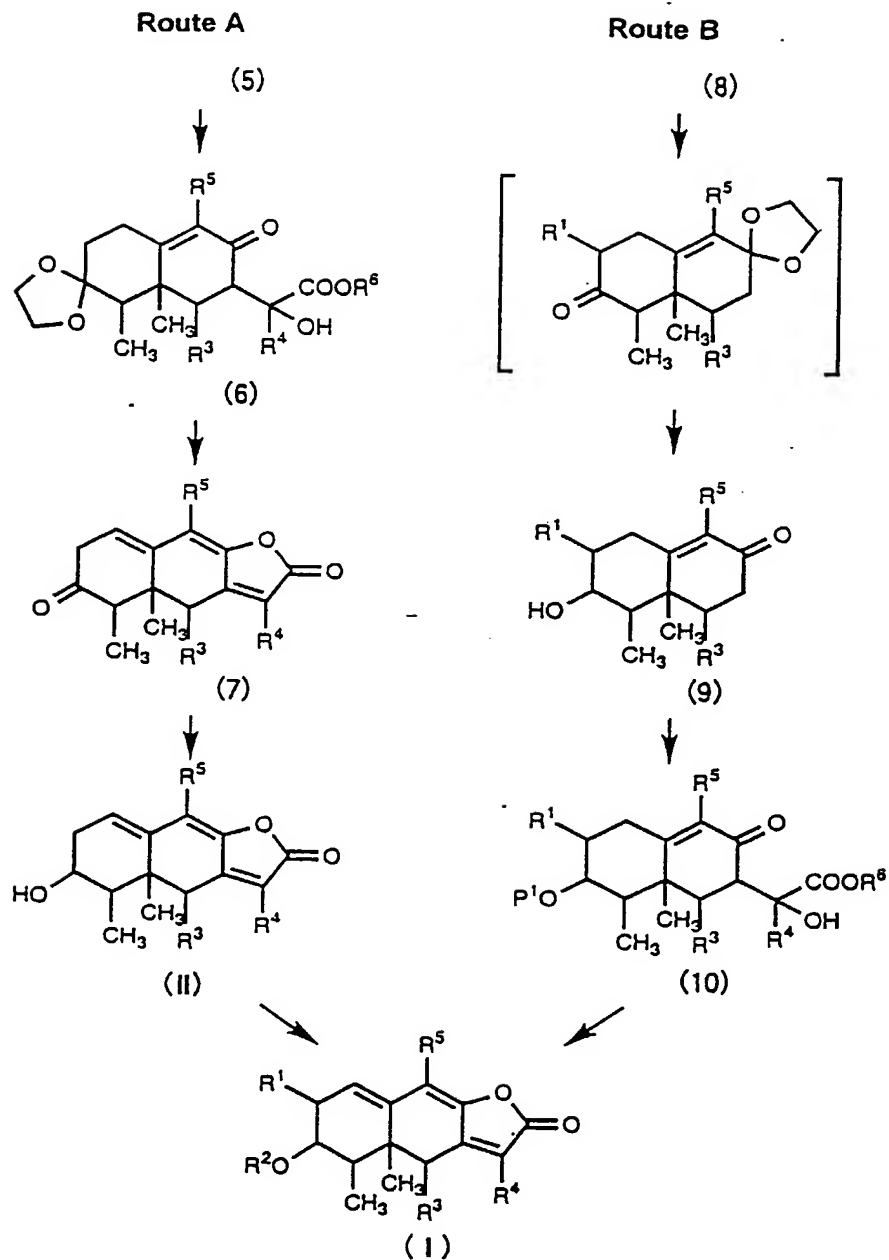
50

55

Scheme 1-1



Scheme 1-2



A compound (1) (vinyltrimethylsilane) is converted to a halide in the presence of a base, and the halide is then reacted with magnesium to give a Grignard reagent. The Grignard reagent is then reacted with an aldehyde to give an alcohol compound which is then oxidized to give a compound (2) wherein R⁵ is as defined above in connection with the formula (I). Halogenating agents usable for the halogenation include bromine, chlorine, and iodine, and the amount of

the halogenating agent used is preferably 1 to 2 equivalents. Bases usable herein include organic bases such as diethylamine, and the amount of the organic base used is preferably 1 to 5 equivalents. The halogenation may be carried out at -78 to 0°C for 1 to 24 hr. Aldehydes usable in the subsequent Grignard reaction include acetaldehyde and propionaldehyde, and the amount of the aldehyde used is preferably 1 to 2 equivalent. The reaction may be carried out in a solvent, such as THF or ether, at 80 to 120°C for 1 to 6 hr. The oxidation may be any commonly used oxidation, and a preferred example thereof is oxidation with Jones' reagent.

Then, a compound (4), wherein R⁵ is as defined above in connection with the formula (I), is synthesized as follows. Specifically, the compound (2) and a compound (3) described in a literature (Liebigs Ann. Chem., 186-190, 1982) are subjected to Michael addition in the presence of an alkyl lithium, such as methyl lithium to give a coupling compound which is then cyclocondensed with a base to give the compound (4). In the compound (4), two methyl groups are sterically regulated to cis configuration. In the Michael addition, the amount of the alkyl lithium used is preferably 1 to 3 equivalents, and solvents usable in this reaction include aprotic solvents, such as ether, THF, and dimethoxyethane, with dimethoxyethane being preferred. The reaction may be carried out at a temperature of -78 to 0°C for 30 min to 6 hr. In the subsequent cyclocondensation, 1 to 3 equivalents of a metal alcoholate, such as sodium methoxide, is preferably used as the base. The reaction may be carried out at 0 to 100°C for 30 min to 6 hr.

The compounds represented by the formula (I) are synthesized via synthesis route A or B depending upon R¹. Specifically, in the case of compounds wherein R¹ is a substituent introduced by a carbon-carbon bond, the compounds are synthesized via the synthesis route B, while the other compounds are synthesized via the synthesis route A.

20 Synthesis route A

A compound (5), wherein R³ and R⁵ are as defined above in connection with the formula (I), may be synthesized as follows. Specifically, the compound (4) is regioselectively dehydrogenated to give a $\Delta^{1,4}$ -diene form which is then subjected to a Michael addition reaction with an organocopper reagent to give a compound (5) with an alkyl group introduced thereinto. For the above dehydrogenation, 1 to 3 equivalents of DDQ is preferably used. The reaction may be carried out in a solvent, such as toluene, benzene, xylene, or dioxane, at a temperature of 30 to 150°C for 5 to 24 hr. For the Michael addition reaction, the amount of the organocopper reagent used is preferably 3 to 10 equivalents. The reaction may be carried out in an aprotic solvent, such as ether or THF, at a temperature of -50 to 0°C for 15 to 20 min. For compounds wherein R³ represents a hydrogen atom, this step is omitted, and steps after the compound (4) are carried out.

A compound (6), wherein R³, R⁴, and R⁵ are as defined above in connection with the formula (I) and R⁶ represents a hydrogen atom or C₁-C₆ lower alkyl, may be synthesized as follows. The compound (5) is condensed with a keto ester in the presence of a base and optionally a catalytic amount of zinc chloride by aldol condensation to give the compound (6). When R⁴ in the compound (6) represents alkyl, organic bases commonly used in conventional aldol reactions may be used as the base. For example, use of 1 to 3 equivalents of lithium diisopropylamide is preferred. Further, addition of a catalytic amount of dried zinc chloride is preferred. The reaction may be carried out in a solvent, such as THF or ether, at a temperature of -78 to 0°C for 30 min to 6 hr. On the other hand, when R⁴ represents a hydrogen atom, preferred bases include water-soluble inorganic bases, such as sodium hydroxide and potassium hydroxide, with use of a large excess amount of water-soluble sodium hydroxide being more preferred. The reaction may be carried out in an alcohol solvent (preferably ethanol) at a temperature of 20 to 100°C for 30 min to 6 hr.

A compound (7), wherein R³, R⁴, and R⁵ are as defined above in connection with the formula (I), may be prepared by heating the compound (6) in the presence of an acid catalyst. The acid catalyst is preferably an organic acid, such as 0.1 to several equivalents of p-toluenesulfonic acid. The reaction may be carried out in a solvent, such as benzene or xylene, preferably toluene, at a temperature of 0 to 100°C for 30 min to 6 hr.

Compounds represented by the formula (II) may be prepared by a reduction of the compound (7) with sodium borohydride. The hydroxyl group at the 6-position of the resultant compounds is generally of β configuration. Reducing agents usable herein include lithium borohydride and tetrabutylammonium borohydride. Among them, sodium borohydride is preferred. The amount of the reducing agent used is 1 to 5 equivalents. The reaction may be carried out in an alcohol solvent (preferably methanol) at a temperature of -10 to 50°C for several min to 3 hr.

Conversion of the compound represented by the formula (II) to the compound represented by the formula (I) may be carried out as follows.

At the outset, introduction of a hydroxyl group into the 7-position of the compound represented by the formula (II) may be carried out by oxidation with an oxidizing agent (for example, selenium dioxide, DDQ, or manganese dioxide with a large excess amount of selenium dioxide being preferred) in a solvent (for example, dioxane, acetic acid, ethanol, t-butanol, or water with dioxane being preferred). In general, the hydroxyl group at the 7-position of the resultant compound is generally of β configuration. The reaction may be carried out at a temperature of 20 to 60°C for one hr to several days.

The hydroxyl group at the 6- and 7-positions of the compound thus obtained may be reacted in the same manner

as described above in connection with the reaction using substance PF1092C as a starting compound to give the compound represented by the formula (I).

Synthesis route B

A compound (8), wherein R^3 and R^5 are as defined above in connection with the formula (I), may be prepared by deketalizing the compound (4) and then introducing a regioselective protective group into the enone. The deketalization may be carried out using an aqueous sodium perchlorate solution or an inorganic acid, such as hydrochloric acid or sulfuric acid, with use of 0.1 to 1.0 equivalent of an aqueous sodium perchlorate solution being preferred. The reaction may be carried out in a solvent (for example, methylene chloride, chloroform, benzene, or toluene) at a temperature of -25 to 25°C for 1 to 5 hr. The protection of the enone may be generally carried out with a reagent used for the conventional acetalization, and use of 1 to 5 equivalents of 1,2-bis(trimethylsilyloxy)ethane is preferred. In the reaction, addition of a catalytic amount of trimethylsilyltrifluoromethane sulfonate is preferred. The reaction may be carried out in a solvent (for example, methylene chloride, chloroform or toluene with methylene chloride being preferred) at a temperature of -78 to 0°C for 3 to 7 days.

A compound (9), wherein R^1 , R^3 , and R^5 are as defined above in connection with the formula (I), may be prepared by reacting the compound (8) with an alkyl halide in the presence of a base to alkylate the α position of the ketone and subsequently conducting a reduction and deprotection. Bases usable in the alkylation include those used in the conventional alkylation. The base is preferably lithium diisopropylamide, and the amount thereof is preferably 1 to 2 equivalents. The alkylation may be carried out in a solvent, such as THF or ether, at a temperature of -78 to 25°C for 2 to 6 hr. The reduction may be carried out with a reducing agent, such as lithium borohydride, sodium borohydride, or tetrabutylammonium borohydride, and use of 1 to 5 equivalents of lithium borohydride is preferred. The reaction may be carried out in an alcohol solvent (preferably methanol) at a temperature of -10 to 50°C for 6 to 14 hr. Acid catalysts usable in the subsequent deprotection include organic acids such as p-toluenesulfonic acid, and the amount thereof is preferably 0.1 to 1 equivalent. The reaction may be carried out in a solvent (for example, acetone, benzene, xylene, or toluene with acetone being preferred) at a temperature of 0 to 50°C for 30 min to 2 hr.

A compound (10), wherein R^3 , R^4 , and R^5 are as described above in connection with the formula (I), R^6 represents a hydrogen atom or lower alkyl and P^1 represents a protective group for the hydroxyl group, may be prepared as follows. At the outset, the hydroxyl group of the compound (9) is protected. Protective groups usable herein include conventional protective groups used for the hydroxyl group, and β -methoxyethoxymethyl (MEM) is preferred with the amount thereof being preferably 5 to 10 equivalents. The reaction may be carried out in a solvent (for example, DMF or dioxane with DMF being preferred) at a temperature of 0 to 50°C for 20 to 40 hr. Subsequently, the protected compound is condensed with α -keto ester by aldol condensation in the presence of a base and optionally a catalytic amount of zinc chloride to give the compound (10). Bases usable herein include organic bases used in conventional aldol reaction, and lithium diisopropylamide is preferred with the amount thereof being preferably 1 to 3 equivalents. The zinc chloride is preferably a catalytic amount of dried zinc chloride from the viewpoint of yield. The reaction may be carried out in a solvent, such as THF or ether, at a temperature of -78 to 0°C for 30 min to 6 hr.

The resultant compound (10) may be heated in the presence of an acid catalyst to give the compound represented by the formula (I). Acid catalysts usable herein include organic acids such as p-toluenesulfonic acid with the amount thereof being preferably 0.1 to several equivalents. The reaction may be carried out in a solvent (for example, benzene, toluene, or xylene with benzene being preferred) at a temperature of 0 to 100°C for 30 min to 6 hr. Thereafter, the protective group for the hydroxyl group at the 6-position is removed, and the hydroxyl group may be reacted in the same manner as described above in connection with the reaction using substance PF1092C as a starting compound to give the compound represented by the formula (I).

(h) Total synthesis of compounds represented by formula (I) (part 2)

According to still another embodiment of the present invention, total synthesis of substance PF1092C as described in the following scheme has been established, permitting total synthesis of the compounds represented by the formula (I). The synthesis will be described in the order of description of the scheme.

Scheme 2

5

10

15

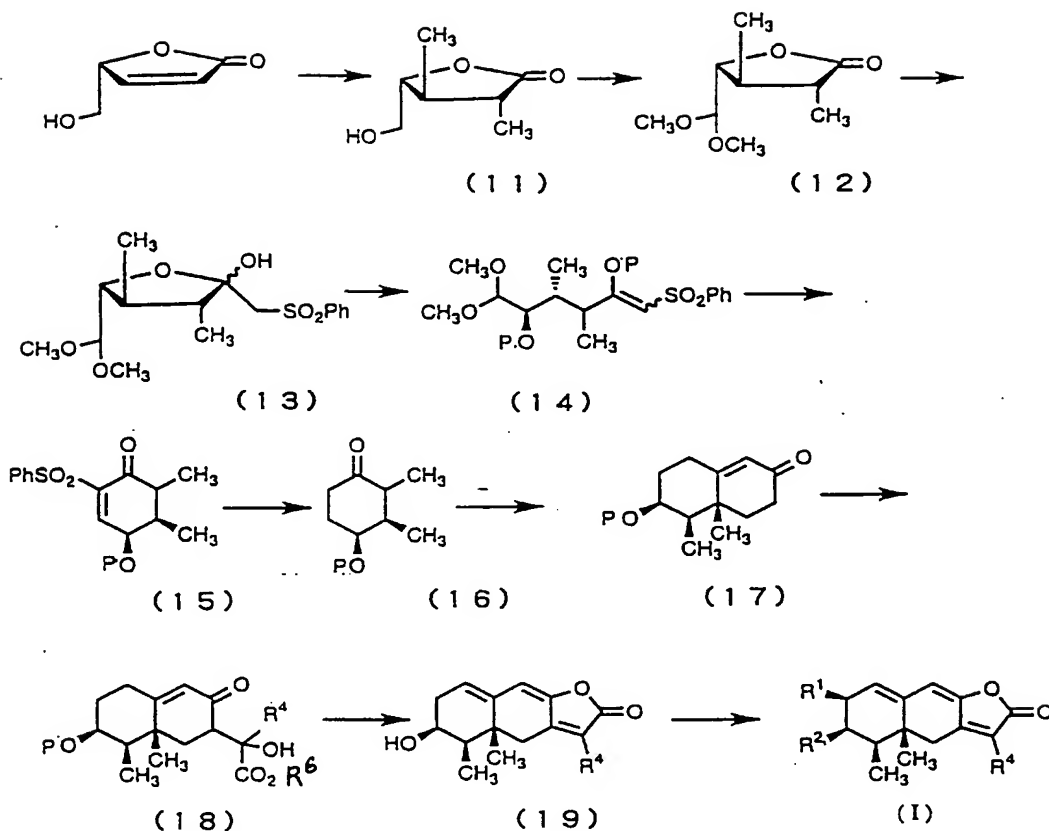
20

25

30

35

40



In the process represented by the above scheme, (R)-(+)-5-hydroxymethyl-2(5)-furanone is used as a starting compound.

At the outset, the hydroxyl group at the 6-position of the starting compound is protective with a protective group (for example, trityl group), and the compound is then reacted with a copper reagent, such as methylcopper lithium, to introduce methyl into the 4-position. Thereafter, methyl iodide is added thereto in the presence of lithiumbistrimethylsilylamide to introduce a methyl group at the α position (3-position) of the carbonyl. The protective group is then removed by known means to give a compound (11). Subsequently, the hydroxyl group in the compound (11) is oxidized, for example, with dimethylsulfoxide to give an aldehyde which is then subjected to acetal protection using, for example, methyl orthoformate to give a compound (12).

The compound (12) is then reacted with benzenesulfonylmethyl in the presence of a base to give a benzenesulfonyl compound (13). Preferably, one to two equivalents of an organic base, such as n-butyllithium, is used as the base. The reaction may be carried out in a solvent (for example, THF or diethyl ether) at a temperature of -78 to 0°C for 30 min to 6 hr.

A compound (14), wherein P represents a protective group for a hydroxyl group, may be prepared by protecting the hydroxyl group of the compound (13) with a protective group, such as t-butyldimethylsilyl and then conducting a ring-opening reaction in the presence of a base. Silylating agents usable herein include t-butyldimethylsilyl chloride and t-butyldimethylsilyltrifluoromethane sulfonate, and use of 1.5 to 5 equivalents of t-butyldimethylsilyltrifluoromethane sul-

fonate is preferred. Preferred bases include organic bases such as triethylamine and 2,6-lutidine and imidazole with 3 to 10 equivalents of 2,6-lutidine being preferred. The reaction may be carried out in a solvent (for example, THF, diethyl ether or methylene chloride with THF being preferred) at a temperature of 0 to 50°C for 10 to 20 hr.

The compound (14) is then subjected to a ring-closing reaction with a Lewis acid to give a cyclohexenone (15) with two asymmetric centers. The Lewis acid is preferably tin tetrachloride with the amount thereof being preferably 1 to 2 equivalents. The reaction may be carried out in a solvent (for example, acetonitrile, benzene, toluene, or methylene chloride with methylene chloride being preferred) at a temperature of -78 to 0°C for 1 to 5 hr.

The double bond of the compound (15) is reduced to give a compound (16). Preferred reducing agents include aluminum-mercury amalgam with the amount thereof being preferably 10 to 20 equivalents. The reaction may be carried out in a solvent (for example, diethyl ether or THF with diethyl ether being preferred) at a temperature of 0 to 25°C for 1 to 5 hr.

The resultant compound (16) and 3-trimethylsilyl-3-buten-2-one may be subjected to Michael addition and cyclocondensation in the presence of a base to give a bicyclic compound (17) with two methyl groups being sterically regulated to cis configuration. An alkyl lithium, such as methyl lithium, is used as a reagent in the Michael addition, and use thereof in an amount of 1 to 3 equivalents is preferred. The reaction may be carried out in an aprotic solvent, such as diethyl ether, THF, or dimethoxyethane, preferably dimethoxyethane, at a temperature of -78 to 0°C for 30 min to 6 hr. The subsequent cyclocondensation may be carried out in the presence of a base (for example, a metal alcoholate, such as sodium methoxide, with the amount thereof being preferably 1 to 3 equivalents) at a temperature of 0 to 100°C for 30 min to 6 hr.

Subsequently, the compound (17) is condensed with α -keto ester by aldol condensation in the presence of a base and optionally a catalytic amount of zinc chloride to give a compound (18) wherein R^4 is as defined above in connection with the formula (I). Bases usable herein include those used in conventional aldol reaction, and use of 1 to 3 equivalents of lithiumdimethylsilylamide is preferred. The zinc chloride is preferably a catalytic amount of dried zinc chloride from the viewpoint of yield. The reaction may be carried out in a solvent, such as THF or ether, at a temperature of -78 to 0°C for 30 min to 6 hr.

The compound (18) may be heated under reflux in the presence of an acid catalyst to give a compound (19). Acid catalysts usable in the ring-closing reaction include organic acids, such as camphorsulfonic acid, with the amount thereof being preferably 0.1 to several equivalents. The reaction may be carried out in a solvent (for example, 1,4-dioxane, benzene, or toluene with 1,4-dioxane being preferred) at a temperature of 0 to 150°C for 15 to 48 hr.

The introduction of a hydroxyl group into the 7-position of the compound (19) may be carried out by oxidation with an oxidizing agent (for example, selenium dioxide, DDQ, or manganese dioxide with a large excess amount of selenium dioxide being preferred) in a solvent (for example, 1,4-dioxane, acetic acid, ethanol, t-butanol, or water with 1,4-dioxane being preferred). In general, the hydroxyl group at the 7-position of the resultant compound is generally of β configuration. The reaction may be carried out at a temperature of 30 to 100°C for one hr to several days.

The hydroxyl group at the 6- and 7-positions of the compound thus obtained may be reacted in the same manner as described above in connection with the reaction using substance PF1092C as a starting compound to give the compound represented by the formula (I).

(i) Resolution of racemic compounds

The compounds represented by the formula (I) according to the present invention may exist as the above various isomers, and racemic derivatives may be resolved by optical resolution using a chiral column. Chiral columns usable herein include a polymer stationary phase column, a protein stationary phase column, and a cellulosic stationary phase column. A preferred mobile phase usable herein is phosphate buffer-acetonitrile for the protein stationary phase column and hexane-isopropanol for the cellulosic stationary phase column.

Substance PF1092

The starting material of the above process for the production of the compound of the formula (I) may be prepared by culturing strain PF 1092 described below.

1. Mycological properties of strain PF1092

(1) Cultural characteristics:

It forms a colony of 30 to 40 mm in diameter on Czapek yeast extract agar medium after culturing at 25°C for 7 days. The colony is white and funiclose, and forms conidia scatteringly. Backside of the colony becomes light brown. It grows well on malt extract agar medium, and diameter of its colony reaches 40 to 45 mm after culturing at 25°C for 7

days. The colony is white and funiculose, forms conidia slightly and produces light brown extract. Backside of the colony becomes light mud yellow. At 37 °C, its growth and formation of conidia are superior to those at 25°C on all media.

(2) Morphological characteristics:

Conidiophore stands straight almost vertically from aerial mycelium, is rough-surfaced and has a size of 30-70 x 2.5-8.5 µm. Penicilli are monovericillate. Four to eight phialides are formed on conidiophore, each being needle-like and having smooth to slightly rough surface and a size of 8-10 x 2.5-3.0 µm. Conidium is globose to subglobose, flat with slightly depressed sides, and has smooth surface and a size of 2.0-2.5 µm.

On the basis of the above mycological characteristics, this strain was identified as the genus Penicillium.

This strain has been deposited in National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology, as international deposition number under Budapest Treaty; FERM BP-5350.

As can be found in other fungi, strain PF1092 is apt to change its properties. For example, not only strain PF1092 but also all of its mutant strains (spontaneous or induced mutants), zygotes and genetic recombinants can be used, provided that they can produce substances PF1092.

2. A method of culturing substance PF1092 producing strain

The substance PF1092 producing strain is cultured using a medium containing nutrients which can be utilized by ordinary microorganisms. As the nutrient sources, known materials conventionally used for the culturing of fungi can be used. Examples of usable carbon sources include glucose, sucrose, starch syrup, dextrin, starch, glycerol, molasses, animal and plant oils and the like. Examples of usable nitrogen sources include soybean meal, wheat germ, corn steep liquor, cotton seed meal, meat extract, peptone, yeast extract, ammonium sulfate, sodium nitrate, urea and the like. In addition to these nutrients, it is effective to add inorganic salts which can release sodium, potassium, calcium, magnesium, cobalt, chlorine, phosphate, sulfate and the like ions as occasion demands. Also, certain organic and inorganic substances which can assist the fungal growth and enhance the production of substances PF1092 may be added properly.

Preferably, the culturing may be carried out under aerobic conditions, particularly by static culturing using a rice medium or by submerged culturing. Suitable culturing temperature is 15 to 40 °C, but the culturing is carried out at about 26 to 37 °C in most cases. Though it varies depending on the medium and culturing conditions employed, accumulation of produced substances PF1092 reaches its maximum generally after 10 to 20 days of culturing in the case of static culturing using a rice medium or generally after 2 to 10 days of shaking or fermentor culturing. The culturing is completed when maximum accumulation of substances PF1092 is obtained, and the desired substance is isolated and purified from the culture broth.

3. Purification of substances PF1092

Substances PF1092 thus obtained by the present invention can be extracted and purified from the cultured mixture making use of its properties by usual separation means such as solvent extraction, ion exchange resin method, absorption or partition chromatography; gel filtration, dialysis, precipitation and the like, alone or in an appropriate combination. For example, substances PF1092 can be extracted with acetone-water or ethyl acetate after culturing using a rice medium. In order to further purify substances PF1092, a chromatography may be carried out using an adsorbent such as silica gel (for example, Wakogel C-200 manufactured by Wako Pure Chemical Industries), alumina or the like or Sephadex LH-20 (manufactured by Pharmacia), Toyo Pearl HW-40SF (manufactured by Tosoh) or the like.

By carrying out such techniques alone or in an optional combination, highly purified substance PF1092A, substance PF1092B and substance PF1092C are obtained. Physico-chemical properties and chemical structures of the thus obtained substances PF1092A, PF1092B and PF1092C are as follows.

1. Physico-chemical properties and chemical structure of substance PF1092A:

(1) Color and shape: colorless needle crystals

(2) Molecular formula: $C_{17}H_{20}O_5$

(3) Mass spectrum (FD-MS): m/z 304 (M)⁺

(4) Specific rotation: $[\alpha]_D = -10.86^\circ$ (c 0.5, $CHCl_3$)

(5) Ultraviolet ray absorption spectrum

λ_{max} : 322 (17,500) nm(ε) (in methanol)

(6) Infrared absorption spectrum: measured in KBr tablet (see Fig. 1)

(7) ¹HNMR Spectrum: measured in $CDCl_3$ solution (see Fig. 2) (PPm): 5.97 (1H), 5.66 (1H), 5.28 (1H), 4.53 (1

EP 0 885 893 A1

H), 2.83 (1H), 2.19(3H), 2.18 (1H), 2.05 (OH), 1.97 (1H), 1.91 (3H), 1.15(3H), 1.10(8H)

(8) ^{13}C NMR Spectrum: measured in CDCl_3 solution (see Fig. 8)

(PPm): 171.8 (s), 170.9 (s), 149.3 (s), 146.3 (s), 140.4 (s), 128.7 (d), 122.3 (s), 107.7 (d), 73.6 (d), 68.2 (d), 40.2 (d), 37.8 (s), 35.6 (t), 21.0 (q), 20.9 (q), 12.7 (q), 8.6 (q)

(9) Solubility: soluble in chloroform, acetone, ethyl acetate, methanol and dimethyl sulfoxide, and insoluble in water and hexane

(10) Basic, acidic or neutral: neutral substance

(11) Rf Value by silica gel thin layer chromatography (TLC) : 0.25 in hexane-ethyl acetate (1:1) developing solvent

Based on the above physico-chemical properties and X-ray crystallographic analysis, the chemical structure of the substance PF1092A was determined as the compound of the formula (I) wherein R^1 is OH, R^2 is $\text{CH}_3\text{COO}-$, R^3 and R^5 are H, and R^4 is CH_3 .

2. Physico-chemical properties and chemical structure of substance PF1092B:

(1) Color and shape: colorless needle crystals

(2) Molecular formula: $\text{C}_{17}\text{H}_{20}\text{O}_5$

(3) Mass spectrum (FD-MS): m/z 304 (M^+)

(4) Specific rotation: $[\alpha]_{\text{D}}^{24} = -110.22^\circ$ (± 0.5 , CHCl_3)

(5) Ultraviolet ray absorption spectrum λ_{max} : 320 (15,100) nm(e) (in methanol)

(6) Infrared absorption spectrum: measured in KBr tablet (see Fig. 4)

(7) ^1H NMR Spectrum: measured in CDCl_3 solution (see Fig. 5)

(PPm): 5.95 (1H), 5.57 (1H), 5.46 (1H), 4.05 (1H), 2.84 (1H), 2.18(1H), 2.15 (3H), 1.97 (OH), 1.91 (3H), 1.83 (1H), 1.23 (3H), 1.22 (3H)

(8) ^{13}C NMR Spectrum: measured in CDCl_3 solution (see Fig. 6)

(PPm): 170.9 (s), 170.2 (s), 149.5 (s), 146.7 (s), 142.4 (s), 124.5 (d), 122.4 (s), 107.4 (d), 72.5 (d), 70.5 (d), 41.0 (d), 38.1 (s), 35.8 (t), 21.4 (q), 21.2 (q), 12.8 (q), 8.6 (q)

(9) Solubility: soluble in chloroform, acetone, ethyl acetate, methanol and dimethyl sulfoxide, and insoluble in water and hexane

(10) Basic, acidic or neutral: neutral substance

(11) Rf Value by silica gel thin layer chromatography (TLC): 0.42 in hexane-ethyl acetate (1:1) developing solvent

Based on the above physico-chemical properties and X-ray crystallographic analysis, the chemical structure of the substance PF1092A was determined as the compound of the formula (I) wherein R^1 is $\text{CH}_3\text{COO}-$, R^2 is OH, R^3 and R^5 are H, and R^4 is CH_3 .

3. Physico-chemical properties and chemical structure of substance PF1092C:

(1) Color and shape: colorless needle crystals

(2) Molecular formula: $\text{C}_{15}\text{H}_{18}\text{O}_4$

(3) Mass spectrum (FD-MS): m/z 262 (M^+)

(4) Specific rotation: $[\alpha]_{\text{D}}^{24} = -96.36^\circ$ (± 0.5 , CHCl_3)

(5) Ultraviolet ray absorption spectrum λ_{max} : 324 (14,900) nm(e) (in methanol)

(6) Infrared absorption spectrum: measured in KBr tablet (see Fig. 7)

(7) ^1H NMR Spectrum: measured in CDCl_3 solution (see Fig. 8)

(ppm): 5.96 (1H), 5.64 (1H), 4.37 (1H), 3.93 (1H), 2.83 (1H), 2.22 (OH), 2.20 (OH), 2.17(1H), 1.91 (3H), 1.24 (3H), 1.20 (3H)

(8) ^{13}C NMR Spectrum: measured in CDCl_3

(ppm): 171.0 (s), 149.3 (s), 146.7 (s), 141.0 (s), 129.1 (d), 122.1 (s), 107.8 (d), 72.4 (d), 69.0 (d), 40.3 (d), 37.9 (s), 35.8 (t), 21.5 (q), 13.0 (q), 8.5 (q)

(9) Solubility: soluble in chloroform, acetone, ethyl acetate, methanol and dimethyl sulfoxide, and insoluble in water and hexane

(10) Basic, acidic or neutral: neutral substance

(11) Rf Value by silica gel thin layer chromatography (TLC): 0.20 in hexane-ethyl acetate (1:1) developing solvent

Based on the above physico-chemical properties and X-ray crystallographic analysis, the chemical structure of the substance PF1092A was determined as the compound of the formula (I) wherein R^1 and R^2 are OH, R^3 and

R⁵ are H, and R⁴ is CH₃.

EXAMPLES

5 The present invention will be described in more detail with reference to the following examples, though it is not limited to these examples only.

Example A1

10 (4aR,5R,6R,7S)-6-Hydroxy-7-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (15 mg, 0.06 mmol) was dissolved in methylene chloride (0.3 ml). Diisopropylethylamine (25 µl, 0.14 mmol) and propionyl chloride (11 µl, 0.13 mmol) were added to the solution under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was then stirred for additional 17 hr. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to prepare the title compound (8.2 mg, 45%).

20 ¹H NMR (CDCl₃) δ 1.19 (t, J = 7.5 Hz, 3H), 1.24 (s, 3H), 1.25 (d, J = 7.0 Hz, 3H), 1.86 (dq, J = 7.0, 1.7 Hz, 1H), 1.92 (d, J = 1.7 Hz, 3H), 2.20 (br d, J = 16.3 Hz, 1H), 2.44 (q, J = 7.5 Hz, 2H), 2.86 (d, J = 16.3 Hz, 1H), 4.06 (m, 1H), 5.49 (m, 1H), 5.58 (br s, 1H), 5.97 (s, 1H); MS (EI) m/z 318 (M)⁺.

Example A2

25 (4aR,5R,6R,7S)-7-Hydroxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (9.9 mg, 0.04 mmol) was dissolved in methylene chloride (0.2 ml). To the solution were added 4-dimethylaminopyridine (4.5 mg, 0.04 mmol) and propionyl chloride (8 µl, 0.09 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was then stirred for additional 22 hr. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to give the title compound (4.9 mg, 41%).

35 ¹H NMR (CDCl₃) δ 1.12 (d, J = 7.1 Hz, 3H), 1.18 (d, J = 0.6 Hz, 3H), 1.18 (t, J = 7.6 Hz, 3H), 1.93 (d, J = 1.8 Hz, 3H), 2.01 (dq, J = 7.1, 1.6 Hz, 1H), 2.21 (br d, J = 16.4 Hz, 1H), 2.43, 2.43 (each q, J = 7.6 Hz, 2H), 2.85 (d, J = 16.4 Hz, 1H), 4.56 (m, 1H), 5.31 (ddd, J = 5.1, 1.6, 1.6 Hz, 1H), 5.68 (br s, 1H), 6.00 (s, 1H); MS (EI) m/z 318 (M)⁺.

Example A3

40 (4aR,5R,6R,7S)-6-(2-Furancarbonyloxy)-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

(1) Substance PF1092C (19 mg, 0.07 mmol) was dissolved in anhydrous DMF (0.4 ml). Imidazole (50 mg, 0.73 mmol) and t-butyldimethylsilyl chloride (65 mg, 0.43 mmol) were added to the solution, and the mixture was stirred at 25°C for 7 hr. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (toluene : ethyl acetate = 10 : 1) to prepare a corresponding 7-O-(t-butyldimethylsilyl) derivative (23 mg, 85%).

50 (2) The compound (21 mg, 0.06 mmol) prepared in the above step (1) was dissolved in methylene chloride (0.45 ml). To the solution were added 4-dimethylaminopyridine (34 mg, 0.27 mmol) and 2-furoyl chloride (24 µl, 0.24 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was then stirred for additional 22 hr. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (toluene : ethyl acetate = 20 : 1) to prepare a corresponding 7-O-(t-butyldimethylsilyl)-6-O-(2-furoyl) derivative (23 mg, 89%).

(3) The compound (18 mg, 0.04 mmol) prepared in the above step (2) was dissolved in anhydrous THF (0.5 ml). To

the solution was added a 1.0 M tetrabutylammonium fluoride-THF solution (47 μ l, 0.47 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to prepare the title compound (5.9 mg, 42%).

^1H NMR (CDCl_3) δ 1.18 (d, J = 7.1 Hz, 3H), 1.28 (s, 3H), 1.94 (d, J = 1.6 Hz, 3H), 2.10 (dq, J = 7.1, 1.7 Hz, 1H), 2.25 (br d, J = 16.1 Hz, 1H), 2.89 (d, J = 16.1 Hz, 1H), 4.63 (m, 1H), 5.52 (ddd, J = 5.0, 1.7, 1.7 Hz, 1H), 5.73 (br s, 1H), 6.03 (s, 1H), 6.53 (dd, J = 3.6, 1.6 Hz, 1H), 7.20 (br d, J = 3.6 Hz, 1H), 7.60 (m, 1H); MS (EI) m/z 356 (M) $^+$.

Example A4

(4aR,5R,6R,7S)-6-7-Dipropionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (16 mg, 0.06 mmol) was dissolved in methylene chloride (0.35 ml). To the solution were added 4-dimethylaminopyridine (38 mg, 0.31 mmol) and propionyl chloride (24 μ l, 0.28 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was then stirred for additional 18 hr. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (toluene: ethyl acetate = 5 : 1) to give the title compound (20 mg, 85%).

^1H NMR (CDCl_3) δ 1.10 (d, J = 7.1 Hz, 3H), 1.14 (t, J = 7.6 Hz, 3H), 1.17 (t, J = 7.6 Hz, 3H), 1.21 (d, J = 0.9 Hz, 3H), 1.94 (d, J = 1.7 Hz, 3H), 2.06 (dq, J = 7.1, 1.8 Hz, 1H), 2.24 (br d, J = 16.2 Hz, 1H), 2.30, 2.31 (each q, J = 7.6 Hz, 2H), 2.39 (q, J = 7.6 Hz, 2H), 2.87 (d, J = 16.2 Hz, 1H), 5.41 (m, 1H), 5.58 (br s, 1H), 5.64 (m, 1H), 5.99 (s, 1H); MS (SIMS) m/z 375 ($\text{M}+\text{H}$) $^+$.

Example A5

Substance PF1092C (30 mg, 0.11 mmol) was dissolved in methylene chloride (0.6 ml). To the solution were added diisopropylethylamine (100 μ l, 0.57 mmol) and propionic anhydride (294 μ l, 2.29 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was then stirred for additional 15 hr. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane: ethyl acetate = 1 : 1) to give the compound of Example A1 (19 mg, 52%), the compound of Example A2 (6.0 mg, 16%), and the compound of Example A4 (3.9 mg, 9%).

Example A6a

(4aR,5R,6R,7S)-6-Hydroxy-7-(n-propyl)carbamoyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (18 mg, 0.07 mmol) was dissolved in anhydrous DMF (0.4 ml). n-Propyl isocyanate (325 μ l, 3.47 mmol) was added to the solution, and the mixture was stirred at 100°C for 4 hr. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 2) to prepare the title compound (9.1 mg, 38%).

^1H NMR (CDCl_3) δ 0.95 (t, J = 7.3 Hz, 3H), 1.24 (s, 3H), 1.25 (d, J = 7.3 Hz, 3H), 1.56 (seq, J = 7.3 Hz, 2H), 1.86 (dq, J = 7.3, 1.8 Hz, 1H), 1.93 (d, J = 1.8 Hz, 3H), 2.21 (br d, J = 16.0 Hz, 1H), 2.86 (d, J = 16.0 Hz, 1H), 3.19 (m, 2H), 4.09 (m, 1H), 4.86 (m, 1H), 5.40 (m, 1H), 5.62 (s, 1H), 5.97 (s, 1H); MS (EI) m/z 347 (M) $^+$.

Example A6b(4aR,5R,6R,7S)-7-Hydroxy-6-(n-propyl)carbamoyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

In Example A6a, the title compound (2.0 mg, 8%), together with the compound described in Example A6a, was obtained.

¹H NMR (CDCl₃) δ 0.93 (t, J = 7.4 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.55 (m, 2H), 1.93 (d, J = 1.5 Hz, 3H), 1.97 (br q, J = 7.2 Hz, 1H), 2.19 (br d, J = 16.9 Hz, 1H), 2.85 (d, J = 16.9 Hz, 1H), 3.18 (m, 2H), 4.54 (m, 1H), 4.79 (m, 1H), 5.12 (m, 1H), 5.66 (br s, 1H), 5.98 (s, 1H); MS (EI) m/z 347 (M)⁺.

Example A6c(4aR,5R,6R,7S)-6,7-di[(n-propyl)carbamoyloxy]-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

In Example A6a, the title compound (4.3 mg, 14%), together with the compound described in Example A6a and the compound described in Example A6b, was obtained.

¹H NMR (CDCl₃) δ 0.93 (t, J = 7.3 Hz, 3H), 0.93 (t, J = 7.7 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 1.17 (s, 3H), 1.53 (m, 4H), 1.93 (d, J = 1.3 Hz, 3H), 2.02 (br q, J = 6.4 Hz, 1H), 2.23 (br d, J = 16.2 Hz, 1H), 2.86 (d, J = 16.2 Hz, 1H), 3.15 (m, 4H), 5.31 (m, 1H), 5.51 (m, 1H), 5.66 (br s, 1H), 5.98 (s, 1H), 6.20 (m, 2H); MS (SIMS) m/z 455 (M+Na)⁺.

Example A7(4aR,5R,6R,7S)-7-Benzoyloxy-6-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (9.7 mg, 0.04 mmol) was dissolved in toluene (0.2 ml). To the solution were added 60% sodium hydride (31 mg, 0.78 mmol) and benzyl bromide (132 μl, 1.11 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was then stirred for additional 2 days. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 50 : 1) to give the title compound (5.3 mg, 41%).

¹H NMR (CDCl₃) δ 1.24 (s, 3H), 1.70 (br q, J = 7.2 Hz, 1H), 1.77 (d, J = 7.2 Hz, 3H), 1.92 (d, J = 1.8 Hz, 3H), 2.15 (br d, J = 16.3 Hz, 1H), 2.85 (d, J = 16.3 Hz, 1H), 4.06 (m, 1H), 4.15 (m, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 5.70 (s, 1H), 5.97 (s, 1H), 7.30-7.40 (m, 5H); MS (FD) m/z 352 (M)⁺.

Example A8(4aR,5R,6R,7S)-6-Benzoyloxy-7-methoxymethoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

(1) Substance PF1092C (50 mg, 0.19 mmol) was dissolved in methylene chloride (1.0 ml). To the solution were added diisopropylethylamine (40 μl, 0.23 mmol) and methoxymethyl chloride (17 μl, 0.22 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was stirred for additional 15 hr. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (chloroform : methanol = 50 : 1) to prepare a corresponding 7-O-methoxymethyl derivative (24 mg, 42%).

(2) The compound (20 mg, 0.07 mmol) prepared in the above step (1) was dissolved in methylene chloride (0.4 ml). To the solution were added 4-dimethylaminopyridine (12 mg, 0.12 mmol) and benzoyl chloride (9 μl, 0.09 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was then raised to 25°C, and the mixture was stirred for additional 22 hr. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (toluene : ethyl acetate = 5 : 1) to give the title compound (13 mg, 49%).

EP 0 885 893 A1

¹H NMR (CDCl₃) δ 1.18 (d, J = 7.1 Hz, 3H), 1.28 (br s, 3H), 1.94 (d, J = 1.7 Hz, 3H), 2.10 (dq, J = 7.1, 1.8 Hz, 1H), 2.26 (br d, J = 16.3 Hz, 1H), 2.90 (d, J = 16.3 Hz, 1H), 3.36 (s, 3H), 4.54 (d, J = 7.0 Hz, 1H), 4.57 (m, 1H), 4.81 (d, J = 7.0 Hz, 1H), 5.71 (ddd, J = 4.8, 1.8, 1.8 Hz, 1H), 5.76 (br s, 1H), 6.07 (s, 1H), 7.45 (m, 2H), 7.57 (m, 1H), 8.02 (m, 2H); MS (EI) m/z 410 (M)⁺.

Example A9

(4aR,5R,6R,7S)-7-Hydroxy-6-(2-tetrahydropyranyloxy)-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (8.9 mg, 0.03 mmol) was dissolved in methylene chloride (0.2 ml). p-Toluenesulfonic acid monohydrate (21 mg, 0.11 mmol) and 3,4-dihydro-2H-pyran (15 μl, 0.16 mmol) were added to the solution, and the mixture was stirred at 25°C for 30 min. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (chloroform : methanol = 40 : 1) to give the title compound (isomer mixture, 4.2 mg, 36%).

¹H NMR (CDCl₃) δ 1.18 (d, J = 0.5 Hz, 3H), 1.29 (d, J = 7.1 Hz, 3H), 1.46-1.73 (m, 6H), 1.91 (dq, J = 7.1, 3.1 Hz, 1H), 1.94 (d, J = 2.1 Hz, 3H), 2.22 (br d, J = 16.4 Hz, 1H), 2.84 (d, J = 16.4 Hz, 1H), 3.67 (t, J = 6.2 Hz, 2H), 4.15 (dd, J = 6.9, 3.1 Hz, 1H), 4.59 (dd, J = 6.9, 3.8 Hz, 1H), 4.92 (t, J = 4.7 Hz, 1H), 5.75 (d, J = 3.8 Hz, 1H), 5.96 (s, 1H); MS (EI) m/z 346 (M)⁺.

¹H NMR (CDCl₃) δ 1.16 (d, J = 0.8 Hz, 3H), 1.29 (d, J = 7.2 Hz, 3H), 1.46-1.73 (m, 6H), 1.84 (dq, J = 7.2, 2.3 Hz, 1H), 1.94 (d, J = 2.1 Hz, 3H), 2.21 (br d, J = 16.2 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H), 3.65 (t, J = 6.4 Hz, 2H), 4.18 (dd, J = 6.0, 2.3 Hz, 1H), 4.80 (dd, J = 6.0, 3.3 Hz, 1H), 4.97 (t, J = 4.7 Hz, 1H), 5.67 (d, J = 3.3 Hz, 1H), 5.96 (s, 1H); MS (EI) m/z 346 (M)⁺.

Example A10

(4aR,5R,6R,7R)-7-Methoxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

(1) Substance PF1092C (200 mg, 0.76 mmol) was dissolved in methylene chloride (4.0 ml). Diisopropylethylamine (237 μl, 1.36 mmol) and methanesulfonyl chloride (88 μl, 1.14 mmol) were added to the solution at -15°C, and the mixture was stirred at the same temperature for 30 min. Methanol (153 μl, 3.78 mmol) was then added thereto, the temperature was raised to 25°C, and the mixture was then stirred for additional 45 min. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1) to prepare a corresponding 7α-methoxy derivative (110 mg, 52%).

(2) The compound (11 mg, 0.04 mmol) prepared in the above step (1) was dissolved in methylene chloride (0.25 ml). To the solution was added 4-dimethylaminopyridine (25 mg, 0.21 mmol) and propionyl chloride (16 μl, 0.16 mmol) under ice cooling, and the mixture was stirred under ice cooling for 30 min. The temperature was raised to 25°C, and the mixture was then stirred for additional 3 hr. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (toluene : ethyl acetate = 4 : 1) to prepare the title compound (5.7 mg, 42%).

¹H NMR (CDCl₃) δ 1.12 (d, J = 7.1 Hz, 3H), 1.14 (s, 3H), 1.16 (t, J = 7.5 Hz, 3H), 1.93 (d, J = 1.7 Hz, 3H), 2.10 (dq, J = 7.1, 2.8 Hz, 1H), 2.25 (br d, J = 16.4 Hz, 1H), 2.36 (q, J = 7.5 Hz, 2H), 2.86 (d, J = 16.4 Hz, 1H), 3.52 (s, 3H), 3.61 (dd, J = 4.7, 1.4 Hz, 1H), 5.11 (ddd, J = 2.8, 1.4, 1.4 Hz, 1H), 5.84 (br d, J = 4.7 Hz, 1H), 6.00 (s, 1H); MS (FAB) m/z 333 (M+H)⁺.

Example A11a

(4aR,5R,6R,7S)-6-Acetylamino-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (102 mg, 0.39 mmol) was dissolved in anhydrous acetonitrile (4.0 ml). To the solution was

added 2-acetoxyisobutyl bromide (0.51 ml, 3.49 mmol), and the mixture was stirred at 25°C for 30 min. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and a saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 4) to give a corresponding 2'-methyloxazoline derivative (54 mg, 49%).

The compound (54 mg, 0.19 mmol) prepared just above was dissolved in pyridine (1.9 ml), water (0.48 ml) and p-toluenesulfonic acid monohydrate (31 mg, 0.17 mmol) were added to the solution, and the mixture was stirred at 100°C for 1.5 hr. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (methylene chloride : methanol = 10 : 1) to give the title compound (6.4 mg, 11%).

¹H NMR (CDCl₃) δ 1.12 (s, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.93 (d, J = 1.7 Hz, 3H), 2.01 (dq, J = 7.1, 2.8 Hz, 1H), 2.07 (s, 3H), 2.20 (br d, J = 16.3 Hz, 1H), 2.87 (d, J = 16.3 Hz, 1H), 4.45 (m, 1H), 4.64 (m, 1H), 5.51 (br d, J = 9.5 Hz, 1H), 5.69 (br s, 1H), 6.00 (s, 1H); MS (FAB) m/z 302 (M-H)⁺.

Example A11b

(4aR,5R,6R,7R)-6-Acetylamino-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

In Example A11a, the title compound (4.8 mg, 8%), together with the compound described in Example A11a, was obtained.

¹H NMR (CDCl₃) δ 1.09 (s, 3H), 1.13 (d, J = 7.2 Hz, 3H), 1.94 (d, J = 1.7 Hz, 3H), 2.03 (s, 3H), 2.28 (dq, J = 7.2, 4.0 Hz, 1H), 2.32 (br d, J = 16.5 Hz, 1H), 2.86 (d, J = 16.5 Hz, 1H), 4.14-4.20 (m, 2H), 5.49 (m, 1H), 5.88 (br d, J = 4.7 Hz, 1H), 6.02 (s, 1H); MS (FAB) m/z 302 (M-H)⁺.

Example A12

(4aR,5R,6R,7S)-6-Chloroacetoxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (10 mg, 40%) was prepared in the same manner as in Example A2, except that substance PF1092C (19 mg, 0.07 mmol), 4-dimethylaminopyridine (9.0 mg, 0.07 mmol), and chloroacetyl chloride (14 µl, 0.18 mmol) were stirred at 25°C for 19 hr and the purification was performed by preparative TLC (chloroform : methanol = 40 : 1).

¹H NMR (CDCl₃) δ 1.15 (d, J = 7.2 Hz, 3H), 1.18 (s, 3H), 1.93 (d, J = 1.4 Hz, 3H), 2.05 (dq, J = 7.2, 1.8 Hz, 1H), 2.22 (br d, J = 16.2 Hz, 1H), 2.86 (d, J = 16.2 Hz, 1H), 4.15 (s, 2H), 4.59 (m, 1H), 5.38 (m, 1H), 5.67 (br s, 1H), 6.00 (s, 1H); MS (EI) m/z 338 (M)⁺.

Example A13

(4aR,5R,6R,7S)-7-Hydroxy-6-phenylacetoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (9.4 mg, 34%) was prepared in the same manner as in Example A5, except that substance PF1092C (19 mg, 0.07 mmol), diisopropylethylamine (32 µl, 0.18 mmol), and phenylacetyl chloride (24 µl, 0.18 mmol) were stirred at 25°C for 16 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1).

¹H NMR (CDCl₃) δ 0.97 (d, J = 0.8 Hz, 3H), 1.00 (d, J = 7.2 Hz, 3H), 1.90 (d, J = 1.9 Hz, 3H), 1.95 (dq, J = 7.2, 1.8 Hz, 1H), 2.16 (br d, J = 16.3 Hz, 1H), 2.79 (d, J = 16.3 Hz, 1H), 3.70 (s, 1H), 3.71 (s, 1H), 4.49 (m, 1H), 5.28 (ddd, J = 5.1, 1.8, 1.8 Hz, 1H), 5.62 (br s, 1H), 5.96 (s, 1H), 7.28 (m, 5H); MS (SIMS) m/z 381 (M+H)⁺.

Example A14

(4aR,5R,6R,7S)-6-(2-Furancarboxyloxy)-7-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (70 mg, 90%) was prepared in the same manner as in Example A3, except that the compound (60 mg, 0.19 mmol) prepared in Example A1, 4-dimethylaminopyridine (103 mg, 0.84 mmol), and 2-furoyl chloride (74 µl, 0.75 mmol) were stirred at 25°C for 30 min and the purification was performed by column chromatography on silica gel (toluene : ethyl acetate = 10 : 1).

¹H NMR (CDCl₃) δ 1.07 (t, J = 7.5 Hz, 3H), 1.17 (d, J = 7.1 Hz, 3H), 1.32 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H), 2.16 (dq,

EP 0 885 893 A1

J = 7.1, 1.8 Hz, 1H), 2.26 (q, J = 7.5 Hz, 2H), 2.28 (br d, J = 16.7 Hz, 1H), 2.91 (d, J = 16.7 Hz, 1H), 5.59 (ddd, J = 4.8, 1.8, 1.8 Hz, 1H), 5.62 (br s, 1H), 5.73 (m, 1H), 6.03 (s, 1H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 7.17 (br d, J = 3.5, 0.8 Hz, 1H), 7.60 (m, 1H); MS (FAB) m/z 413 (M+H)⁺.

5 Example A15

(4aR,5R,6R,7S)-7-Cyclopropylcarbonyloxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

10 The title compound (70 mg, 96%) was prepared in the same manner as in Example A3, except that the compound (60 mg, 0.19 mmol) prepared in Example A2, anhydrous pyridine (151 μ l, 1.87 mmol), and cyclopropanecarbonyl chloride (68 μ l, 0.75 mmol) were stirred at 25°C for 30 min and the purification was performed by column chromatography on silica gel (toluene : ethyl acetate = 20 : 1).

15 ¹H NMR (CDCl₃) δ 0.89 (m, 2H), 1.02 (m, 2H), 1.10 (d, J = 7.1 Hz, 3H), 1.19 (t, J = 7.6 Hz, 3H), 1.20 (s, 3H), 1.55 (m, 1H), 1.93 (d, J = 1.5 Hz, 3H), 2.05 (dq, J = 7.1, 2.1 Hz, 1H), 2.23 (br d, J = 16.2 Hz, 1H), 2.40 (q, J = 7.6 Hz, 2H), 2.87 (d, J = 16.2 Hz, 1H), 5.43 (m, 1H), 5.59 (m, 1H), 5.60 (br s, 1H), 5.99 (s, 1H); MS (ESI) m/z 387 (M+H)⁺.

Example A16

20 (4aR,5R,6R,7S)-7-Hydroxy-6-(2-methylpropionyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (3.8 mg, 32%) was prepared in the same manner as in Example A5, except that substance PF1092C (9.3 mg, 0.04 mmol), diisopropylethylamine (61 μ l, 0.35 mmol), and isobutyryl chloride (37 μ l, 0.35 mmol) were stirred at 25°C for 19 hr and the purification was performed by preparative TLC (chloroform : methanol = 100 : 1).

25 ¹H NMR (CDCl₃) δ 1.12 (d, J = 7.2 Hz, 3H), 1.18 (s, 3H), 1.23, 1.23 (each d, J = 6.9 Hz, 6H), 1.93 (d, J = 1.8 Hz, 3H), 2.02 (dq, J = 7.2, 2.1 Hz, 1H), 2.22 (br d, J = 16.0 Hz, 1H), 2.66 (sep, J = 6.9 Hz, 1H), 2.86 (d, J = 16.0 Hz, 1H), 4.57 (m, 1H), 5.30 (m, 1H), 5.68 (br s, 1H), 6.00 (s, 1H); MS (EI) m/z 332 (M)⁺.

30 Example A17

(4aR,5R,6R,7S)-6-Cyclopropylcarbonyloxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

35 The procedure of Examples A3 (1) and (2) was repeated, except that 7-O-(t-butyldimethylsilyl) derivative of PF1092C (37 mg, 0.10 mmol), 4-dimethylaminopyridine (59 mg, 0.49 mmol), and cyclopropanecarbonyl chloride (40 μ l, 0.44 mmol) were stirred at 25°C for 17 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 20 : 1). Thus, a corresponding 7-O-(t-butyldimethylsilyl)-6-O-cyclopropylcarbonyl derivative (40 mg, 93%) was prepared.

40 Further, the procedure of Example A3 (3) was repeated, except that the compound (40 mg, 0.09 mmol) prepared just above and a 1.0 M solution of tetrabutylammonium fluoride in THF (100 μ l, 0.10 mmol) were stirred at 25°C for 2 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1). Thus, the title compound (15 mg, 51%) was prepared.

45 ¹H NMR (CDCl₃) δ 0.93 (m, 2H), 1.05 (m, 2H), 1.13 (d, J = 7.1 Hz, 3H), 1.20 (s, 3H), 1.65 (m, 1H), 1.93 (d, J = 1.7 Hz, 3H), 2.00 (dq, J = 7.1, 1.8 Hz, 1H), 2.21 (br d, J = 16.0 Hz, 1H), 2.81 (d, J = 16.0 Hz, 1H), 4.55 (m, 1H), 5.30 (ddd, J = 5.0, 1.8, 1.8 Hz, 1H), 5.69 (br s, 1H), 6.00 (s, 1H); MS (EI) m/z 330 (M)⁺.

Example A18

50 (4aR,5R,6R,7S)-7-Cyclohexylcarbonyloxy-6-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (5.2 mg, 41%) was prepared in the same manner as in Example A1, except that substance PF1092C (8.9 mg, 0.03 mmol), diisopropylethylamine (15 μ l, 0.09 mmol), and cyclohexanecarbonyl chloride (10 μ l, 0.07 mmol) were stirred at 25°C for 5 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 8 : 1).

¹H NMR (CDCl₃) δ 1.24 (br s, 3H), 1.25 (d, J = 7.3 Hz, 3H), 1.28-2.00 (m, 10H), 1.86 (dq, J = 7.3, 1.8 Hz, 1H), 1.93 (d, J = 1.6 Hz, 3H), 2.21 (br d, J = 16.4 Hz, 1H), 2.41 (m, 1H), 2.87 (d, J = 16.4 Hz, 1H), 4.05 (m, 1H), 5.48 (m, 1H).

5.56 (br s, 1H), 5.97 (s, 1H); MS (EI) m/z 372 (M)⁺.

Example A19

5 (4aR,5R,6R,7S)-6-Cyclohexylcarbonyloxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (6.2 mg, 48%) was prepared in the same manner as in Example A2, except that substance PF1092C (9.0 mg, 0.03 mmol), 4-dimethylaminopyridine (4.4 mg, 0.04 mmol), and cyclohexanecarbonyl chloride (11 μl, 0.08 mmol) were stirred at 25°C for 6 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 8 : 1).

¹H NMR (CDCl₃) δ 1.11 (d, J = 7.1 Hz, 3H), 1.19 (br s, 3H), 1.22-1.96 (m, 10H), 1.93 (d, J = 1.7 Hz, 3H), 2.01 (dq, J = 7.1, 1.9 Hz, 1H), 2.21 (br d, J = 16.3 Hz, 1H), 2.39 (m, 1H), 2.85 (d, J = 16.3 Hz, 1H), 4.55 (m, 1H), 5.30 (ddd, J = 5.2, 1.9, 1.9 Hz, 1H), 5.68 (br s, 1H), 6.00 (s, 1H); MS (EI) m/z 372 (M)⁺.

Example A20

(4aR,5R,6R,7S)-6-Cinnamoyloxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

20 The procedure of Examples A3 (1) and (2) was repeated, except that 7-O-(t-butyldimethylsilyl) derivative of PF1092C (30 mg, 0.08 mmol), 4-dimethylaminopyridine (50 mg, 0.41 mmol), and cinnamoyl chloride (120 mg, 0.72 mmol) were stirred at 25°C for 2 days and the purification was performed by preparative TLC (hexane : ethyl acetate = 4 : 1). Thus, a corresponding 7-O-(t-butyldimethylsilyl)-6-O-cinnamonyl derivative (22 mg, 54%) was prepared.

25 Further, the procedure of Example A3 (3) was repeated, except that the compound (22 mg, 0.04 mmol) prepared just above and a 1.0 M solution of tetrabutylammonium fluoride in THF (47 μl, 0.05 mmol) were stirred at 25°C for 2.5 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1). Thus, the title compound (8.6 mg, 52%) was prepared.

30 ¹H NMR (CDCl₃) δ 1.17 (d, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.94 (d, J = 1.7 Hz, 3H), 2.07 (dq, J = 7.1, 1.8 Hz, 1H), 2.24 (br d, J = 16.5 Hz, 1H), 2.88 (d, J = 16.5 Hz, 1H), 4.62 (m, 1H), 5.47 (ddd, J = 5.1, 1.8, 1.8 Hz, 1H), 5.73 (br s, 1H), 6.03 (s, 1H), 6.47 (d, J = 16.0 Hz, 1H), 7.40 (m, 3H), 7.53 (m, 2H), 7.74 (d, J = 16.0 Hz, 1H); MS (TSP) m/z 393 (M+H)⁺.

Example A21

(4aR,5R,6R,7S)-6-Benzoyloxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

35 The title compound (25 mg, 74%) was prepared in the same manner as in Example A5, except that substance PF1092C (24 mg, 0.09 mmol), diisopropylethylamine (64 μl, 0.37 mmol), and benzoic anhydride (202 mg, 0.89 mmol) were stirred at 25°C for 20 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1).

40 ¹H NMR (CDCl₃) δ 1.19 (d, J = 7.2 Hz, 3H), 1.30 (s, 3H), 1.94 (d, J = 1.7 Hz, 3H), 2.14 (dq, J = 7.2, 1.8 Hz, 1H), 2.26 (br d, J = 16.2 Hz, 1H), 2.90 (d, J = 16.2 Hz, 1H), 4.66 (m, 1H), 5.61 (ddd, J = 5.1, 1.8, 1.8 Hz, 1H), 5.75 (br s, 1H), 6.05 (s, 1H), 7.46 (m, 2H), 7.59 (m, 1H), 8.03 (m, 2H); MS (SIMS) m/z 367 (M+H)⁺.

Example A22

45 (4aR,5R,6R,7S)-6-Hydroxy-7-(4-nitrobenzoyloxy)-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (3.8 mg, 24%) was prepared in the same manner as in Example A1, except that substance PF1092C (10 mg, 0.04 mmol), diisopropylethylamine (10 μl, 0.06 mmol), and 4-nitrobenzoyl chloride (9.1 mg, 0.05 mmol) were stirred at 25°C for 22 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1).

50 ¹H NMR (CDCl₃) δ 1.29 (br s, 3H), 1.30 (d, J = 7.1 Hz, 3H), 1.95 (d, J = 1.8 Hz, 3H), 1.95 (dq, J = 7.1, 1.7 Hz, 1H), 2.26 (br d, J = 16.4 Hz, 1H), 2.91 (d, J = 16.4 Hz, 1H), 4.24 (m, 1H), 5.71 (br s, 1H), 5.78 (m, 1H), 6.02 (s, 1H), 8.30 (m, 4H); MS (EI) m/z 411 (M)⁺.

Example A23(4aR,5R,6R,7S)-7-Hydroxy-6-(4-nitrobenzoyloxy)-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

5 The title compound (2.1 mg, 22%) was prepared in the same manner as in Example A2, except that substance PF1092C (9.7 mg, 0.04 mmol), 4-dimethylaminopyridine (4.5 mg, 0.04 mmol), and 4-nitrobenzoyl chloride (8.4 mg, 0.05 mmol) were stirred at 25°C for 22 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1).

10 ¹H NMR (CDCl₃) δ 1.29 (br s, 3H), 1.70 (d, J = 7.2 Hz, 3H), 1.95 (d, J = 1.7 Hz, 3H), 2.17 (dq, J = 7.2, 1.9 Hz, 1H), 2.28 (br d, J = 16.4 Hz, 1H), 2.91 (d, J = 16.4 Hz, 1H), 4.71 (m, 1H), 5.63 (ddd, J = 5.1, 1.9, 1.9 Hz, 1H), 5.74 (br s, 1H), 6.05 (s, 1H), 8.18 (m, 2H), 8.31 (m, 2H); MS (EI) m/z 411 (M)⁺.

Example A24(4aR,5R,6R,7S)-6,7-Di[(2-furancarboxyl)oxy]-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (20 mg, 83%) was prepared in the same manner as in Example A4, except that substance PF1092C (14 mg, 0.05 mmol), 4-dimethylaminopyridine (35 mg, 0.28 mmol), and 2-furoyl chloride (24 μl, 0.24 mmol) were stirred at 25°C for 4 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1).

20 ¹H NMR (CDCl₃) δ 1.20 (d, J = 7.1 Hz, 3H), 1.35 (s, 3H), 1.95 (d, J = 1.7 Hz, 3H), 2.21 (dq, J = 7.1, 1.8 Hz, 1H), 2.30 (br d, J = 16.2 Hz, 1H), 2.93 (d, J = 16.2 Hz, 1H), 5.69 (ddd, J = 4.8, 1.8, 1.8 Hz, 1H), 5.73 (m, 1H), 5.91 (m, 1H), 6.04 (s, 1H), 6.42 (dd, J = 3.5, 1.8 Hz, 1H), 6.53 (dd, J = 3.4, 1.7 Hz, 1H), 6.93 (br d, J = 3.5 Hz, 1H), 7.18 (br d, J = 3.4 Hz, 1H), 7.50 (m, 1H), 7.60 (m, 1H); MS (ESI) m/z 468 (M+NH₄)⁺, 473 (M+Na)⁺.

Example A25(4aR,5R,6R,7S)-7-Hydroxy-6-(4-methyl-5-thiazolylcarbonyloxy)-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

30 The procedure of Examples A3 (1) and (2) was repeated, except that 7-O-(t-butyldimethylsilyl) derivative of PF1092C (40 mg, 0.11 mmol), 4-dimethylaminopyridine (130 mg, 1.07 mmol), and 4-methyl-5-thiazolecarbonyl chloride hydrochloride (99 mg, 0.50 mmol) were stirred at 25°C for 8 hr and the purification was performed by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1). Thus, a corresponding 7-O-(t-butyldimethylsilyl)-6-O-(4-methyl-5-thiazolyl)carbonyl derivative (45 mg, 85%) was prepared.

35 Further, the procedure of Example A3 (3) was repeated, except that the above compound (36 mg, 0.07 mmol) and a 1.0 M solution of tetrabutylammonium fluoride in THF (78 μl, 0.08 mmol) were stirred under ice cooling for 30 min and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 2). Thus, the title compound (10 mg, 37%) was prepared.

40 ¹H NMR (CDCl₃) δ 1.19 (d, J = 7.2 Hz, 3H), 1.25 (s, 3H), 1.94 (d, J = 1.9 Hz, 3H), 2.10 (dq, J = 7.2, 1.9 Hz, 1H), 2.24 (br d, J = 16.3 Hz, 1H), 2.80 (s, 3H), 2.88 (d, J = 16.3 Hz, 1H), 4.64 (m, 1H), 5.50 (ddd, J = 5.1, 1.9, 1.9 Hz, 1H), 5.71 (br s, 1H), 6.02 (s, 1H), 8.78 (s, 1H); MS (ESI) m/z 388 (M+H)⁺.

Example A26(4aR,5R,6R,7S)-6-(1-Benzothiophen-2-ylcarbonyloxy)-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

50 The procedure of Examples A3 (1) and (2) was repeated, except that 7-O-(t-butyldimethylsilyl) derivative of PF1092C (42 mg, 0.11 mmol), 4-dimethylaminopyridine (69 mg, 0.57 mmol), and 1-benzothiophene-2-carbonyl chloride (102 mg, 0.52 mmol) were stirred at 25°C for 22 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 20 : 1). Thus, a corresponding 6-O-(1-benzothiophen-2-ylcarbonyl)-7-O-(t-butyldimethylsilyl) derivative (56 mg, 95%) was prepared.

Further, the procedure of Example A3 (3) was repeated, except that the above compound (56 mg, 0.11 mmol) and hydrogen fluoride-pyridine complex (0.13 ml) were stirred at 25°C for 3 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 3 : 1). Thus, the title compound (36 mg, 82%) was prepared.

55 ¹H NMR (CDCl₃) δ 1.21 (d, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.94 (d, J = 1.7 Hz, 3H), 2.11 (dq, J = 7.1, 1.8 Hz, 1H), 2.23 (br d, J = 16.3 Hz, 1H), 2.89 (d, J = 16.3 Hz, 1H), 4.65 (m, 1H), 5.56 (ddd, J = 5.1, 1.8, 1.8 Hz, 1H), 5.73 (br s, 1H), 6.03 (s, 1H), 7.44 (m, 2H), 7.86 (m, 2H), 8.07 (s, 1H); MS (TSI) m/z 423 (M+H)⁺.

Example A27(4aR,5R,6R,7S)-6-Hydroxy-7-methylcarbamoyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

5 The title compound (3.1 mg, 15%) was prepared in the same manner as in Example A6a, except that substance PF1092C (17 mg, 0.06 mmol) and methyl isocyanate (19 μ l, 0.32 mmol) were stirred at 35°C for 9 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1).

¹H NMR (CDCl₃) δ 1.24 (br s, 3H), 1.25 (d, J = 7.1 Hz, 3H), 1.86 (dq, J = 7.1, 1.7 Hz, 1H), 1.93 (d, J = 1.7 Hz, 3H), 2.21 (br d, J = 16.2 Hz, 1H), 2.85 (d, J = 4.9 Hz, 3H), 2.86 (d, J = 16.2 Hz, 1H), 4.09 (m, 1H), 4.79 (m, 1H), 5.41 (m, 1H), 5.61 (br s, 1H), 5.97 (s, 3H); MS (FD) m/z 319 (M)⁺.

Example A28(4aR,5R,6R,7S)-6,7-Di(phenylcarbamoyloxy)-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

15 The title compound (40 mg, 33%) was prepared in the same manner as in Example A6a, except that substance PF1092C (63 mg, 0.24 mmol), 4-dimethylaminopyridine (3.5 mg, 0.03 mmol), and phenyl isocyanate (260 μ l, 2.39 mmol) were stirred at 25°C for 2 hr and the purification was performed by column chromatography on silica gel (toluene : ethyl acetate = 10 : 1).

20 ¹H NMR (CDCl₃) δ 1.20 (d, J = 7.0 Hz, 3H), 1.21 (s, 3H), 1.94 (br s, 3H), 2.10 (dq, J = 7.0, 1.7 Hz, 1H), 2.25 (br d, J = 16.2 Hz, 1H), 2.89 (d, J = 16.2 Hz, 1H), 5.46 (ddd, J = 4.7, 1.7, 1.7 Hz, 1H), 5.67 (m, 1H), 5.72 (br s, 1H), 6.00 (s, 1H), 6.70 (br s, 1H), 6.86 (br s, 1H), 7.07 (m, 2H), 7.28 (m, 8H), 7.41 (m, 2H); MS (FD) m/z 500 (M)⁺.

Example A29(4aR,5R,6R,7S)-6,7-Dimethoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

25 The title compound (268 mg, 24%) was prepared in the same manner as in Example A7, except that substance PF1092C (1.0 g, 3.83 mmol), 60% sodium hydride (264 mg, 6.61 mmol), and methyl iodide (4.1 ml, 65.9 mmol) in DMF were stirred at 25°C for 1.5 hr and the purification was performed by column chromatography on silica gel (toluene : ethyl acetate = 20 : 1).

30 ¹H NMR (CDCl₃) δ 1.18 (s, 3H), 1.21 (d, J = 7.1 Hz, 3H), 1.91 (d, J = 1.9 Hz, 3H), 1.75 (dq, J = 7.1, 1.7 Hz, 1H), 2.14 (br d, J = 16.3 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H), 3.51 (s, 3H), 3.58 (m, 1H), 3.59 (s, 3H), 3.98 (m, 1H), 5.78 (br s, 1H), 5.98 (s, 1H); MS (ESI) m/z 291 (M+H)⁺.

Example A30(4aR,5R,6R,7S)-6-Acetoxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

40 The procedure of Example A29 was repeated, except that substance PF1092C (19 mg, 0.07 mmol), 60% sodium hydride (4.5 mg, 0.11 mmol), and methyl iodide (36 μ l, 0.57 mmol) were stirred at -15°C for 1 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1). Thus, a corresponding 7-O-methyl derivative (9.0 mg, 47%) was obtained.

45 Further, the procedure of Example A8 was repeated, except that the compound (9.0 mg, 0.03 mmol) prepared just above, 4-dimethylaminopyridine (21 mg, 0.17 mmol), and acetyl chloride (10 μ l, 0.14 mmol) were stirred at 25°C for 3 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1). Thus, the title compound (8.0 mg, 78%) was obtained.

50 ¹H NMR (CDCl₃) δ 1.11 (d, J = 7.2 Hz, 3H), 1.16 (s, 3H), 1.92 (d, J = 1.7 Hz, 3H), 1.95 (dq, J = 7.2, 1.7 Hz, 1H), 2.12 (s, 3H), 2.20 (br d, J = 16.4 Hz, 1H), 2.85 (d, J = 16.4 Hz, 1H), 3.42 (s, 3H), 3.99 (m, 1H), 5.49 (ddd, J = 4.6, 1.7, 1.7 Hz, 1H), 5.71 (br s, 1H), 5.99 (s, 1H); MS (ESI) m/z 319 (M+H)⁺.

Example A31(4aR,5R,6R,7S)-6-(2-Furancarbonyloxy)-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

55 The title compound (17 mg, 91%) was prepared in the same manner as in Example A30, except that a 7-O-methyl derivative of substance PF1092C (14 mg, 0.05 mmol), 4-dimethylaminopyridine (32 mg, 0.26 mmol), and 2-furoyl chlo-

ride (23 μ l, 0.23 mmol) were stirred at 25°C for 14 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1).

¹H NMR (CDCl₃) δ 1.16 (d, J = 7.1 Hz, 3H), 1.26 (d, J = 0.8 Hz, 3H), 1.93 (d, J = 1.7 Hz, 3H), 2.05 (dq, J = 7.1, 1.7 Hz, 1H), 2.24 (br d, J = 16.2 Hz, 1H), 2.88 (d, J = 16.2 Hz, 1H), 3.44 (s, 3H), 4.07 (m, 1H), 5.70 (ddd, J = 4.7, 1.7, 1.7 Hz, 1H), 5.75 (br s, 1H), 6.03 (s, 1H), 6.50 (dd, J = 3.5, 1.8 Hz, 1H), 7.15 (dd, J = 3.5, 0.8 Hz, 1H), 7.58 (dd, J = 1.8, 0.8 Hz, 1H); MS (FAB) m/z 371 (M+H)⁺.

Example A32

(4aR,5R,6R,7S)-7-Methoxy-6-(2-thiophenecarbonyloxy)-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (7.7 mg, 73%) was prepared in the same manner as in Example A30, except that a 7-O-methyl derivative of substance PF1092C (7.5 mg, 0.03 mmol), 4-dimethylaminopyridine (17 mg, 0.14 mmol), and 2-thenoyl chloride (13 μ l, 0.12 mmol) were stirred at 25°C for 15 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1).

¹H NMR (CDCl₃) δ 1.18 (d, J = 7.1 Hz, 3H), 1.28 (s, 3H), 1.94 (d, J = 1.8 Hz, 3H), 2.06 (dq, J = 7.1, 1.8 Hz, 1H), 2.25 (br d, J = 16.2 Hz, 1H), 2.89 (d, J = 16.2 Hz, 1H), 3.44 (s, 3H), 4.08 (ddd, J = 4.7, 1.8, 1.8 Hz, 1H), 5.70 (m, 1H), 5.76 (br s, 1H), 6.05 (s, 1H), 7.11 (dd, J = 5.0, 3.7 Hz, 1H), 7.57 (dd, J = 5.0, 1.1 Hz, 1H), 7.80 (dd, J = 3.7, 1.1 Hz, 1H); MS (FAB) m/z 387 (M+H)⁺.

Example A33

(4aR,5R,6R,7S)-6-Acetoxy-7-(n-propyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The procedure of Example A29 was repeated, except that substance PF1092C (200 mg, 0.76 mmol), 60% sodium hydride (80 mg, 2.0 mmol) and n-propyl iodide (1.0 ml, 10.3 mmol) were stirred at 0°C for 10 min and the purification was performed by column chromatography on silica gel (hexane : ethyl acetate = 6 : 1). Thus, a corresponding 7-O-(n-propyl) derivative (87 mg, 37%) was prepared.

Further, the procedure of Example A30 was repeated, except that the compound (33 mg, 0.11 mmol) prepared just above, anhydrous pyridine (44 μ l, 0.54 mmol), and acetyl chloride (35 μ l, 0.49 mmol) were stirred at 25°C for 8.5 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1). Thus, the title compound (30 mg, 79%) was obtained.

¹H NMR (CDCl₃) δ 0.90 (t, J = 6.9 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.15 (d, J = 0.8 Hz, 3H), 1.55 (seq, J = 6.9 Hz, 2H), 1.91 (d, J = 1.4 Hz, 3H), 1.94 (dq, J = 7.2, 1.7 Hz, 1H), 2.10 (s, 3H), 2.18 (br d, J = 17.1 Hz, 1H), 2.84 (d, J = 17.1 Hz, 1H), 3.38 (q, J = 6.9 Hz, 1H), 3.58 (q, J = 6.9 Hz, 1H), 4.06 (m, 1H), 5.47 (ddd, J = 4.8, 1.7, 1.7 Hz, 1H), 5.70 (br s, 1H), 5.98 (s, 1H); MS (ESI) m/z 347 (M+H)⁺.

Example A34

(4aR,5R,6R,7S)-6-Ethoxycarbonyloxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (5.0 mg, 41%) was prepared in the same manner as in Example A30, except that a 7-O-methyl derivative of substance PF1092C (9.7 mg, 0.04 mmol), 4-dimethylaminopyridine (22 mg, 0.18 mmol), and ethoxycarbonyl chloride (15 μ l, 0.16 mmol) were stirred at 25°C for 19 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1).

¹H NMR (CDCl₃) δ 1.18 (d, J = 0.8 Hz, 3H), 1.18 (d, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.86 (d, J = 1.9 Hz, 3H), 1.94 (dq, J = 7.1, 1.7 Hz, 1H), 2.20 (br d, J = 16.3 Hz, 1H), 2.86 (d, J = 16.3 Hz, 1H), 3.46 (s, 3H), 4.00 (m, 1H), 4.21, 4.22 (each q, J = 7.1 Hz, 2H), 5.26 (ddd, J = 4.6, 1.7, 1.7 Hz, 1H), 5.73 (br s, 1H), 5.99 (s, 1H); MS (EI) m/z 348 (M)⁺.

Example A35

(4aR,5R,6R,7S)-7-Methoxy-6-phenoxy-carbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (6.7 mg, 60%) was prepared in the same manner as in Example A30, except that a 7-O-methyl derivative of substance PF1092C (7.8 mg, 0.03 mmol), 4-dimethylaminopyridine (37 mg, 0.31 mmol), and phenoxy-carbonyl chloride (32 μ l, 0.26 mmol) were stirred at 25°C for 18 hr and the purification was performed by preparative TLC

(toluene : ethyl acetate = 4 : 1).

¹H NMR (CDCl₃) δ 1.13 (s, 3H), 1.24 (d, J = 7.1 Hz, 3H), 1.93 (d, J = 1.7 Hz, 3H), 2.00 (dq, J = 7.1, 1.8 Hz, 1H), 2.21 (br d, J = 16.2 Hz, 1H), 2.88 (d, J = 16.2 Hz, 1H), 3.51 (s, 3H), 4.05 (m, 1H), 5.34 (ddd, J = 4.6, 1.8, 1.8 Hz, 1H), 5.75 (br s, 1H), 6.00 (s, 1H), 7.17-7.41 (m, 3H), 7.38 (m, 2H); MS (EI) m/z 396 (M)⁺.

Example A36

(4aR,5R,6R,7S)-6-Methoxymethoxy-7-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The procedure of Example A8 (1) was repeated, except that substance PF1092C (202 mg, 0.77 mmol), diisopropylethylamine (160 µl, 0.92 mmol) and methoxymethyl chloride (64 µl, 0.84 mmol) were stirred at 25°C for 23 hr and the purification was performed by column chromatography on silica gel (toluene : ethyl acetate = 6 : 1). Thus, a corresponding 6-0-methoxymethyl derivative (35 mg, 18%) was prepared.

Further, the procedure of Example A8 (2) was repeated, except that the compound (18 mg, 0.06 mmol) prepared just above, 4-dimethylaminopyridine (19 mg, 0.15 mmol) and propionyl chloride (11 µl, 0.14 mmol) were stirred at 25°C for 4 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 5 : 1). Thus, the title compound (16 mg, 77%) was obtained.

¹H NMR (CDCl₃) δ 1.18 (t, J = 7.6 Hz, 3H), 1.21 (d, J = 7.1 Hz, 3H), 1.22 (s, 3H), 1.91 (dq, J = 7.1, 1.7 Hz, 1H), 1.92 (d, J = 1.7 Hz, 3H), 2.20 (br d, J = 16.3 Hz, 1H), 2.41, 2.42 (each q, J = 7.6 Hz, 2H), 2.87 (d, J = 16.3 Hz, 1H), 3.42 (s, 3H), 3.96 (m, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 5.51 (m, 1H), 5.60 (br s, 1H), 5.97 (s, 1H); MS (FD) m/z 362 (M)⁺.

Example A37

(4aR,5R,6R,7S)-7-Benzoyloxy-6-methoxymethoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (4.8 mg, 42%) was prepared in the same manner as in Example A36, except that a 6-0-methoxymethyl derivative of substance PF1092C (8.6 mg, 0.03 mmol), 4-dimethylaminopyridine (22 mg, 0.18 mmol), and benzoyl chloride (17 µl, 0.15 mmol) were stirred at 25°C for 18 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 5 : 1).

¹H NMR (CDCl₃) δ 1.25 (d, J = 7.1 Hz, 3H), 1.27 (s, 3H), 1.94 (d, J = 1.4 Hz, 3H), 2.00 (dq, J = 7.1, 1.5 Hz, 1H), 2.25 (br d, J = 16.1 Hz, 1H), 2.89 (d, J = 16.1 Hz, 1H), 3.32 (s, 3H), 4.10 (m, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.73 (d, J = 6.8 Hz, 1H), 5.74 (br s, 1H), 5.75 (m, 1H), 6.02 (s, 1H), 7.46 (m, 2H), 7.60 (m, 1H), 8.10 (m, 2H); MS (SIMS) m/z 411 (M+H)⁺.

Example A38

(4aR,5R,6R,7S)-6-Benzoyloxy-7-(2-methoxyethoxymethoxy)-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The procedure of Example A8 (1) and (2) was repeated, except that substance PF1092C (116 mg, 0.44 mmol), diisopropylethylamine (115 µl, 0.66 mmol) and (2-methoxyethoxy)methyl chloride (76 µl, 0.67 mmol) were stirred at 25°C for 23 hr and the purification was performed by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1). Thus, a corresponding 7-0-(2-methoxyethoxy)methyl derivative (74 mg, 48%) was prepared.

Further, the procedure of Example A8 (3) was repeated, except that the compound (44 mg, 0.13 mmol) prepared just above, 4-dimethylaminopyridine (53 mg, 0.44 mmol) and benzoyl chloride (36 µl, 0.31 mmol) were stirred at 25°C for 24 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 5 : 1). Thus, the title compound (22 mg, 38%) was obtained.

¹H NMR (CDCl₃) δ 1.16 (d, J = 7.1 Hz, 3H), 1.27 (s, 3H), 1.94 (d, J = 1.6 Hz, 3H), 2.10 (dq, J = 7.1, 1.8 Hz, 1H), 2.26 (br d, J = 16.0 Hz, 1H), 2.89 (d, J = 16.0 Hz, 1H), 3.39 (s, 3H), 3.55 (m, 2H), 3.64 (m, 1H), 3.77 (m, 1H), 4.62 (m, 1H), 4.65 (d, J = 7.2 Hz, 1H), 4.88 (d, J = 7.2 Hz, 1H), 5.69 (ddd, J = 4.8, 1.8, 1.8 Hz, 1H), 5.77 (br s, 1H), 6.06 (s, 1H), 7.44 (m, 2H), 7.56 (m, 1H), 8.01 (m, 2H); MS (FD) m/z 454 (M)⁺.

Example A39(4aR,5R,6R,7R)-6-(2-Furancarbonyloxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H))-one

The title compound (7.9 mg, 59%) was prepared in the same manner as in Example A10, except that a 7 α -methoxy derivative of substance PF1092C (10 mg, 0.04 mmol), 4-dimethylaminopyridine (24 mg, 0.19 mmol), and 2-furoyl chloride (16 μ l, 0.16 mmol) were stirred at 25°C for 6 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1).

¹H NMR (CDCl₃) δ 1.18 (d, J = 7.2 Hz, 3H), 1.25 (s, 3H), 1.95 (d, J = 2.0 Hz, 3H), 2.20 (dq, J = 7.2, 2.7 Hz, 1H), 2.28 (br d, J = 16.3 Hz, 1H), 2.90 (d, J = 16.3 Hz, 1H), 3.57 (s, 3H), 3.75 (dd, J = 4.8, 1.4 Hz, 1H), 5.32 (ddd, J = 2.7, 1.4, 1.4 Hz, 1H), 5.87 (br d, J = 4.8 Hz, 1H), 6.03 (s, 1H), 6.52 (dd, J = 3.5, 1.8 Hz, 1H), 7.14 (dd, J = 3.5, 0.8 Hz, 1H), 7.60 (dd, J = 1.8, 0.8 Hz, 1H); MS (ESI) m/z 371 (M+H)⁺.

Example A40(4aR,5R,6R,7R)-7-Ethoxy-6-(2-furancarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H))-one

The procedure of Example A10 (1) was repeated, except that substance PF1092C (26 mg, 0.10 mmol), diisopropylethylamine (31 μ l, 0.18 mmol), and methanesulfonyl chloride (10 μ l, 0.13 mmol) were stirred at -15°C for 30 min, ethanol (29 μ l, 0.49 mmol) was added thereto, the temperature was raised to 25°C, and the mixture was stirred at that temperature for 45 min, and the purification was performed by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1). Thus, a corresponding 7 α -ethoxy derivative (12 mg, 41%) was prepared.

The procedure of Example A10 (2) was repeated, except that the compound prepared just above (10 mg, 0.03 mmol), 4-dimethylaminopyridine (30 mg, 0.25 mmol), and 2-furoyl chloride (20 μ l, 0.20 mmol) were stirred at 25°C for 4 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1). Thus, the title compound (10 mg, 78%) was prepared.

¹H NMR (CDCl₃) δ 1.18 (d, J = 7.1 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.25 (s, 3H), 1.95 (d, J = 1.7 Hz, 3H), 2.23 (dq, J = 2.6, 7.1 Hz, 1H), 2.30 (br d, J = 16.1 Hz, 1H), 2.89 (d, J = 16.1 Hz, 1H), 3.69 (dq, J = 9.5, 7.0 Hz, 1H), 3.84 (dd, J = 4.9, 1.2 Hz, 1H), 3.92 (dq, J = 9.5, 7.0 Hz, 1H), 5.30 (m, 1H), 5.85 (br d, J = 4.9 Hz, 1H), 6.02 (s, 1H), 6.52 (dd, J = 3.6, 1.7 Hz, 1H), 7.13 (br d, J = 3.6 Hz, 1H), 7.60 (m, 1H); MS (ESI) m/z 385 (M+H)⁺.

Example A41(4aR,5R,6R,7R)-7-Ethoxy-6-(2-thiophencarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H))-one

The title compound (14 mg, 86%) was prepared in the same manner as in Example A40, except that a 7 α -ethoxy derivative of substance PF1092C (12 mg, 0.04 mmol), 4-dimethylaminopyridine (35 mg, 0.28 mmol), and 2-thenoyl chloride (26 μ l, 0.24 mmol) were stirred at 25°C for 2 hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 4 : 1).

¹H NMR (CDCl₃) δ 1.20 (d, J = 7.1 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.28 (s, 3H), 1.95 (d, J = 1.9 Hz, 3H), 2.23 (dq, J = 7.0, 2.7 Hz, 1H), 2.31 (br d, J = 16.2 Hz, 1H), 2.90 (d, J = 16.2 Hz, 1H), 3.70 (dq, J = 9.4, 7.0 Hz, 1H), 3.88 (dd, J = 4.7, 1.3 Hz, 1H), 3.94 (dq, J = 9.4, 7.0 Hz, 1H), 5.28 (ddd, J = 2.7, 1.3, 1.3 Hz, 1H), 5.86 (br d, J = 4.7 Hz, 1H), 6.03 (s, 1H), 7.13 (dd, J = 5.0, 3.8 Hz, 1H), 7.58 (dd, J = 5.0, 1.3 Hz, 1H), 7.79 (dd, J = 3.8, 1.3 Hz, 1H); MS (ESI) m/z 401 (M+H)⁺.

Example A42(4aR,5R,6R,7R)-6,7-Dimethoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H))-one

The title compound (3.9 mg, 11%) was prepared in the same manner as in Example A29, except that a 7 α -methoxy derivative of substance PF1092C (35 mg, 0.13 mmol), 60% sodium hydride (14 mg, 0.34 mmol) and methyl iodide (159 μ l, 2.55 mmol) were stirred at -30°C for 2 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 2 : 1).

¹H NMR (CDCl₃) δ 1.10 (s, 3H), 1.19 (d, J = 7.1 Hz, 3H), 1.92 (d, J = 1.9 Hz, 3H), 1.92 (dq, J = 7.1, 3.0 Hz, 1H), 2.20 (br d, J = 16.4 Hz, 1H), 2.84 (d, J = 16.4 Hz, 1H), 3.31 (ddd, J = 3.0, 1.5, 1.5 Hz, 1H), 3.42 (s, 3H), 3.46 (s, 3H), 3.75 (dd, J = 5.0, 1.5 Hz, 1H), 5.90 (br d, J = 5.0 Hz, 1H), 5.99 (s, 1H); MS (FAB) m/z 291 (M+H)⁺.

Example A43(4aR,5R,6R,7R)-7-Methoxy-6-methylsulfonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

5 The title compound (22 mg, 82%) was prepared in the same manner as in Example A10, except that a 7 α -methoxy derivative of substance PF1092C (21 mg, 0.07 mmol), 4-dimethylaminopyridine (15 mg, 0.12 mmol), methanesulfonyl chloride (25 μ l, 0.32 mmol) and triethylamine (48 μ l, 0.34 mmol) were stirred at 25°C for 2 days and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 1).

¹H NMR (CDCl₃) δ 1.09 (br s, 3H), 1.24 (d, J = 7.1 Hz, 3H), 1.93 (d, J = 1.8 Hz, 3H), 2.15 (dq, J = 7.1, 2.6 Hz, 1H),
10 2.24 (br d, J = 16.3 Hz, 1H), 2.86 (d, J = 16.3 Hz, 1H), 3.07 (s, 3H), 3.50 (s, 3H), 3.98 (dd, J = 4.8, 1.7 Hz, 1H), 4.86 (m, 1H), 5.86 (br d, J = 4.8 Hz, 1H), 6.00 (s, 1H); MS (ESI) m/z 355 (M+H)⁺.

Example A44(4aR,5R,6R,7R)-7-Acetoxy-6-(2-furancarboxyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The procedure of Example A10 (1) was repeated, except that substance PF1092C (21 mg, 0.08 mmol), diisopropylethylamine (17 μ l, 0.10 mmol), and methanesulfonyl chloride (8 μ l, 0.10 mmol) were stirred at -15°C for 10 min, potassium acetate (16 mg, 0.16 mmol) and an anhydrous acetonitrile solution (52 μ l) containing 18-crown-6 (1.1 mg, catalytic amount) were then added thereto, the mixture was stirred at 25°C for 5 hr, and the purification was performed by preparative TLC (methylene chloride : methanol = 30 : 1). Thus, a corresponding 7 α -acetoxy derivative (11 mg, 44%) was prepared.

The procedure of Example A10 (2) was repeated, except that the above compound (11 mg, 0.04 mmol), 4-dimethylaminopyridine (21 mg, 0.17 mmol), and 2-furoyl chloride (14 μ l, 0.14 mmol) were stirred at 25°C for 4 hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 3 : 2). Thus, the title compound (9.7 mg, 67%) was prepared.

¹H NMR (CDCl₃) δ 1.18 (d, J = 7.1 Hz, 3H), 1.25 (s, 3H), 1.96 (d, J = 1.8 Hz, 3H), 2.09 (s, 3H), 2.21 (dq, J = 7.1, 2.8 Hz, 1H), 2.32 (br d, J = 16.3 Hz, 1H), 2.92 (d, J = 16.3 Hz, 1H), 5.27 (dd, J = 4.8, 1.5 Hz, 1H), 5.31 (m, 1H), 5.88 (br d, J = 4.8 Hz, 1H), 6.03 (s, 1H), 6.52 (dd, J = 3.5, 1.7 Hz, 1H), 7.15 (br d, J = 3.5 Hz, 1H), 7.60 (m, 1H); MS (FAB) m/z 399 (M+H)⁺.

Example A45(4aR,5R,6R,7R)-7-Hydroxy-6-(2-thiophencarbonyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The procedure of Example A10 was repeated, except that substance PF1092C (50 mg, 0.19 mmol), diisopropylethylamine (43 μ l, 0.25 mmol), and methanesulfonyl chloride (18 μ l, 0.23 mmol) were stirred at -15°C for 10 min, silica gel (250 mg) was then added thereto, the mixture was stirred at 25°C for one hr, and the purification was performed by column chromatography on silica gel (hexane : ethyl acetate = 1 : 2). Thus, a corresponding 7 α -hydroxy derivative (18 mg, 36%) was prepared.

The procedure of Example A3 (1) was repeated, except that the above compound (18 mg, 0.07 mmol), imidazole (12 mg, 0.08 mmol), and t-butyldimethylsilyl chloride (12 mg, 0.08 mmol) were stirred at 25°C for one hr and the purification was performed by preparative TLC (toluene : ethyl acetate = 5 : 1). Thus, a corresponding 7 α -(t-butyldimethylsilyl)oxy derivative (23 mg, 88%) was prepared.

Subsequently, the procedure of Example A3 (2) was repeated, except that the compound (23 mg, 0.06 mmol) prepared just above, 4-dimethylaminopyridine (34 mg, 0.28 mmol), and 2-thenoyl chloride (29 μ l, 0.27 mmol) were stirred at 25°C for 18 hr and the purification was performed by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1). Thus, a corresponding 7 α -(t-butyldimethylsilyl)oxy-3 β -(2-thenoyl)oxide derivative (19 mg, 64%) was prepared.

Further, the procedure of Example A3 (3) was repeated, except that the compound (19 mg, 0.04 mmol) prepared just above and a 1.0 M solution of tetrabutylammonium fluoride in THF (46 μ l, 0.05 mmol) were stirred under ice cooling for one hr and the purification was performed by preparative TLC (hexane : ethyl acetate = 1 : 2). Thus, the title compound (6.1 mg, 42%) was prepared.

¹H NMR (CDCl₃) δ 1.21 (d, J = 7.2 Hz, 3H), 1.27 (br s, 3H), 1.96 (d, J = 1.7 Hz, 3H), 2.28 (dq, J = 7.2, 3.0 Hz, 1H),
55 2.31 (br d, J = 16.5 Hz, 1H), 2.92 (d, J = 16.5 Hz, 1H), 4.33 (m, 1H), 5.15 (ddd, J = 3.0, 1.5, 1.5 Hz, 1H), 5.88 (br d, J = 4.9 Hz, 1H), 6.04 (s, 1H), 7.13 (dd, J = 5.0, 3.8 Hz, 1H), 7.59 (dd, J = 5.0, 1.2 Hz, 1H), 7.80 (dd, J = 3.8, 1.2 Hz, 1H); MS (EI) m/z 372 (M)⁺.

Example A46(4aR,5R,6R,7R)-6-Acetylamino-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound (3.0 mg, 20%) was prepared in the same manner as in Example A11, except that a 2'-methyl-oxazoline derivative of substance PF1092C (14 mg, 0.05 mmol) and methanesulfonic acid (20 μ l, 0.01 mmol) were stirred in methanol at 25°C for 3.5 hr and the purification was performed by preparative TLC (methylene chloride : methanol = 20 : 1).

¹H NMR (CDCl₃) δ 1.09 (d, J = 0.9 Hz, 3H), 1.13 (d, J = 7.2 Hz, 3H), 1.93 (d, J = 1.9 Hz, 3H), 2.02 (s, 3H), 2.20 (dq, J = 7.2, 3.7 Hz, 1H), 2.26 (br d, J = 15.9 Hz, 1H), 2.87 (d, J = 15.9 Hz, 1H), 3.49 (s, 3H), 3.60 (dd, J = 5.1, 1.8 Hz, 1H), 4.37 (m, 1H), 5.39 (br d, J = 8.2 Hz, 1H), 5.88 (br d, J = 5.1 Hz, 1H), 6.01 (s, 1H); MS (ESI) m/z 318 (M+H)⁺.

Reference Example 1

Synthesis of compound (7) (Liebigs Ann. Chem., 186, 1982 and Chem. Pharm. Bull., 28, 3265, 1980)

Compound (3) (4.42 g, 17.5 mmol) was dissolved in ethylene glycol dimethyl ether (17 ml) under an argon gas stream, a 2 M solution of methylolithium in THF (20 ml, 40 mmol) was added at 25°C to the solution, and the mixture was stirred for 2 hr. The reaction solution was cooled to -78°C, a solution of compound (2) (in the structural formula, R⁵ = H) (3.2 g) in ethylene glycol dimethyl ether (15 ml) was added to the cooled reaction mixture, followed by stirring for 2 hr. Thereafter, the temperature of the reaction solution was raised to 25°C, a 0.3 M solution of sodium methoxide in methanol (60 ml, 18 mmol) was added thereto, and the mixture was stirred at that temperature for 30 min. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and then dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give compound (4) (in the structural formula, R⁵ = H) (2.5 g, 65%).

A solution of the above compound (4) (500 mg, 2.1 mmol) dissolved in THF (10 ml) was added to a mixed solution composed of a 2 M solution of lithium diisopropylamide in THF (1.2 ml, 2.4 mmol) and THF (3.0 ml) at -78°C under an argon gas stream, and the mixture was stirred for one hr. Subsequently, a saturated solution of zinc chloride in THF (3 ml) and methyl pyruvate (650 mg, 12.7 mmol) were added thereto, and the mixture was stirred at room temperature for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1) to give compound (6) (in the structural formula, R³=H, R⁴=CH₃, R⁵=H, and R⁶=CH₃) (670 mg, 94%).

The compound (6) (600 mg, 1.7 mmol) prepared just above was dissolved in benzene (50 ml), p-toluenesulfonic acid (220 mg, 0.9 mmol) was added to the solution, and the mixture was heated under reflux for 1.5 hr. The reaction solution was cooled, and a saturated aqueous sodium bicarbonate solution was added thereto, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give compound (7) (in the structural formula, R³ = H, R⁴ = CH₃, and R⁵ = H) (174 mg, 42%).

Example B1

(1) Method A

(4aR*,5R*,6S*)-6-Hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Compound (7) (in the structural formula, R³=H, R⁴=CH₃, and R⁵=H) (100 mg, 0.4 mmol) was dissolved in methanol (25 ml), sodium borohydride (7 mg, 0.18 mmol) was added at 25°C, and the mixture was stirred for 10 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give the title compound (63 mg, 60%).

¹H NMR (CDCl₃) δ 1.16 (d, J = 0.9 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H), 1.74 (dq, J = 7.2, 2.5 Hz, 1H), 1.89 (d, J = 1.4 Hz, 3H), 2.18 (d, J = 16.3 Hz, 1H), 2.40 (dd, J = 20.0, 4.7 Hz, 1H), 2.57 (br ddd, J = 20.0, 3.6 Hz, 1H), 2.82 (d, J = 16.3

EP 0 885 893 A1

Hz, 1H), 4.02 (m, 1H), 5.74 (m, 1H), 5.97(s, 1H); MS (EI) m/z 246 (M)⁺.

(2) Method B

5 (4aR,5R,6S)-6-Hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

Substance PF1092C (500 mg, 1.90 mmol) was dissolved in benzene (50 ml), p-toluenesulfonic acid (250 mg, 1.32 mmol) was added to the solution, and the mixture was stirred at 50°C for 30 min. A saturated aqueous sodium bicarbonate solution was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1) to give compound (7) (in the structural formula, R³ = H, R⁴ = CH₃, and R⁵ = H) (260 mg, 56%).

The compound (7) (in the structural formula, R³ = H, R⁴ = CH₃, and R⁵ = H) was dissolved in methanol (15 ml), sodium borohydride (80.5 mg, 2.17 mmol) was added, and the mixture was stirred for 10 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1) to give the title compound (160 mg, 61%).

20 Example B2

(4aR*,5R*,6S*)-6-Acetoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B1 (in the general formula (II), R³ = H, R⁴ = CH₃, and R⁵ = H) (50 mg, 0.20 mmol) was dissolved in pyridine (5 ml), acetyl chloride (80 mg, 0.70 mmol) was added thereto, and the mixture was stirred at 25°C for one hr. A 15% aqueous potassium hydrogensulfate solution was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give the title compound (55 mg, 80%).

¹H NMR (CDCl₃) δ 1.08 (d, J = 7.2 Hz, 3H), 1.14 (d, J = 0.9 Hz, 3H), 1.89 (dq, J = 7.2, 2.5 Hz, 1H), 1.90 (d, J = 1.4 Hz, 3H), 2.04 (s, 3H), 2.19 (d, J = 16.3 Hz, 1H), 2.38 (dd, J = 20.0, 4.7 Hz, 1H), 2.58 (br ddd, J = 20.0, 3.6 Hz, 1H), 2.84 (d, J = 16.3 Hz, 1H), 5.12 (m, 1H), 5.70 (m, 1H), 5.96 (s, 1H); MS (EI) m/z 288(M)⁺.

Example B3

35 (1) Method A

(4aR*,5R*,6S*)-6-Propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 was reacted with propionyl chloride.

¹H NMR (CDCl₃) δ 1.08 (d, J = 7.2 Hz, 3H), 1.13 (t, J = 7.5 Hz, 3H), 1.14 (s, 3H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 1.91 (d, J = 1.4 Hz, 3H), 2.21 (d, J = 16.3 Hz, 1H), 2.33 (q, J = 7.5 Hz, 2H), 2.38 (dd, J = 20.0, 4.7 Hz, 1H), 2.59 (br ddd, J = 20.0, 3.6 Hz, 1H), 2.84 (d, J = 16.3 Hz, 1H), 5.14 (m, 1H), 5.70 (m, 1H), 5.97 (s, 1H); MS (EI) m/z 302(M)⁺.

45 (2) Method B

(4aR,5R,6S)-6-Propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 (2) Method B was reacted with propionyl chloride.

Example B4

55 (4aR*,5R*,6S*)-6-Butyryloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 was reacted with butyryl chloride.

EP 0 885 893 A1

¹H NMR (CDCl₃) δ 0.93 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H), 1.14 (d, J = 0.9 Hz, 3H), 1.64 (seq, J = 7.2 Hz, 2H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 1.90 (d, J = 1.4 Hz, 3H), 2.21 (d, J = 16.3 Hz, 1H), 2.28 (t, J = 7.2 Hz, 2H), 2.37 (dd, J = 20.0, 4.7 Hz, 1H), 2.59 (br ddd, J = 20.0, 3.6 Hz, 1H), 2.84 (d, J = 16.3 Hz, 1H), 5.14 (m, 1H), 5.70 (br t, 1H), 5.97 (s, 1H); MS (EI) m/z 316(M)⁺.

Example B5

(4aR*,5R*,6S*)-6-(2-Methyl)propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 was reacted with isobutyryl chloride.

¹H NMR (CDCl₃) δ 1.08 (d, J = 7.1 Hz, 3H), 1.14 (d, J = 7.2 Hz, 3H), 1.15 (d, J = 0.9 Hz, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.90 (d, J = 1.4 Hz, 3H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 2.21 (d, J = 16.3 Hz, 1H), 2.34 (dd, J = 20.0, 4.7 Hz, 1H), 2.53 (sep, J = 7.1 Hz, 1H), 2.59 (br dd, J = 20.0, 3.6 Hz, 1H), 2.84 (d, J = 16.3 Hz, 1H), 5.12 (m, 1H), 5.70 (br t, 1H), 5.97 (s, 1H); MS (EI) m/z 316(M)⁺.

Example B6

(4aR*,5R*,6S*)-6-(3-Methyl)butyryloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 was reacted with isovaleryl chloride.

¹H NMR (CDCl₃) δ 0.93 (d, J = 6.5 Hz, 6H), 1.08 (d, J = 7.2 Hz, 3H), 1.14 (s, 3H), 1.90 (d, J = 1.4 Hz, 3H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 2.09 (m, 1H), 2.18 (d, J = 6.5 Hz, 2H), 2.21 (d, J = 16.3 Hz, 1H), 2.37 (dd, J = 20.0, 4.7 Hz, 1H), 2.59 (br dd, J = 20.0, 3.6 Hz, 1H), 2.84 (d, J = 16.3 Hz, 1H), 5.13 (m, 1H), 5.70 (br t, 1H), 5.97 (s, 1H); MS (EI) m/z 330(M)⁺.

Example B7

(4aR*,5R*,6S*)-6-Benzoyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 was reacted with benzoyl chloride.

¹H NMR (CDCl₃) δ 1.17 (d, J = 7.2 Hz, 3H), 1.30 (s, 3H), 1.92 (d, J = 1.4 Hz, 3H), 2.03 (dq, J = 7.2, 2.5 Hz, 1H), 2.27 (d, J = 16.3 Hz, 1H), 2.54 (dd, J = 20.0, 4.7 Hz, 1H), 2.73 (br ddd, J = 20.0, 3.6 Hz, 1H), 2.89 (d, J = 16.3 Hz, 1H), 5.41 (m, 1H), 5.75 (br t, 1H), 6.00 (s, 1H), 7.40-8.11 (m, 5H); MS (EI) m/z 350(M)⁺.

Example B8

(1) Method A

(4aR*,5R*,6S*)-6-(2-Furoyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 was reacted with 2-furoyl chloride.

¹H NMR (CDCl₃) δ 1.16 (d, J = 7.2 Hz, 3H), 1.27 (s, 3H), 1.93 (d, J = 1.7 Hz, 3H), 2.00 (dq, J = 7.2, 2.5 Hz, 1H), 2.26 (d, J = 16.4 Hz, 1H), 2.54 (br dd, J = 20.8, 5.0 Hz, 1H), 2.69 (br ddd, 1H), 2.88 (d, J = 16.4 Hz, 1H), 5.38 (br t, 1H), 5.74 (br t, 1H), 5.96 (s, 1H), 6.50 (dd, J = 3.3, 1.7 Hz, 1H), 7.11 (dd, J = 3.3, 0.8 Hz, 1H), 7.57 (dd, J = 1.7, 0.8 Hz, 1H); MS (EI) m/z 340 (M)⁺.

(2) Method B

(4aR,5R,6S)-6-(2-Furoyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 (2) Method B was reacted with 2-furoyl chloride.

Example B9(4aR*,5R*,6S*)-4a,5,6,7-Tetrahydro-6-(2-thenoyl)oxy-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B2, except that the compound prepared in Example B1 was reacted with 2-thenoyl chloride.

¹H NMR (CDCl₃) δ 1.16 (d, J = 7.2 Hz, 3H), 1.27 (s, 3H), 1.92 (d, J = 1.4 Hz, 3H), 2.03 (dq, J = 7.2, 2.5 Hz, 1H), 2.25 (d, J = 16.3 Hz, 1H), 2.54 (dd, J = 20.0, 4.7 Hz, 1H), 2.69 (br ddd, J = 20.0, 3.6 Hz, 1H), 2.87 (d, J = 16.3 Hz, 1H), 5.33(m, 1H), 5.73 (br t, 1H), 5.99 (s, 1H), 7.09 (dd, J = 5.0, 3.7 Hz, 1H), 7.54 (dd, J = 1.3, 5.0 Hz, 1H), 7.76 (dd, J = 3.7, 1.3 Hz, 1H); MS (FAB) m/z 357(M+H)⁺.

Example B10(6'R*,7'R*)-Spiro[1,3-dioxolane-2,8'-(2',6',7'-trimethylbicyclo[4.4.0]deca-1'-en-3'-one)]

compound (3) (400 mg, 1.6 mmol) was dissolved in ethylene glycol dimethyl ether (10 ml) under an argon gas stream, a 1 M solution of methylolithium in diethyl ether (2 ml, 2 mmol) was added to the solution, and the mixture was stirred at 25°C for 2 hr. The reaction mixture was cooled to -78°C, a solution of compound (2) (in the structural formula, R⁵ = CH₃) (250 mg, 1.6 mmol) in ethylene glycol dimethyl ether (5 ml) was added to the cooled reaction mixture, followed by stirring for 2 hr. Thereafter, the temperature of the reaction solution was raised to 25°C, a 0.3 M solution of sodium methoxide in methanol (6 ml, 2 mmol) was added thereto, and the mixture was stirred at room temperature for 30 min. Water (20 ml) was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and then dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1) to give the title compound (230 mg, 59%).

¹H NMR (CDCl₃) δ 0.92 (d, J = 6.9 Hz, 3H), 1.22 (s, 3H), 1.50 (ddd, J = 17.4, 14.5, 4.1 Hz, 1H), 1.68 (br ddd, J = 19.1, 13.9, 5.1 Hz, 1H), 1.75 (q, J = 6.9 Hz, 1H), 1.80 (br s, 3H), 1.95-2.06 (m, 2H), 2.30-2.50(m, 3H), 2.71 (dd, J = 14.5, 3.7 Hz, 1H), 3.84-4.09 (m, 4H); MS (ESI) m/z 251(M+H)⁺.

Example B11(4'S*,6'R*,7'R*)-Spiro[1,3-dioxolane-2,8'-(4'-(1"-hydroxy-1"-methoxycarbonyl)ethyl-2',6',7'-trimethylbicyclo[4.4.0]deca-1'-en-3'-one)]

A 2 M solution of lithium diisopropylamide in THF (0.5 ml, 1.0 mmol) was added to anhydrous THF (1 ml) at -78°C under an argon gas stream, a THF solution (2 ml) containing the compound prepared in Example B10 (200 mg, 0.8 mmol) was added thereto, and the mixture was stirred for one hr. Subsequently, a saturated solution of zinc chloride in THF (1 ml) and an anhydrous THF solution (2 ml) containing methyl pyruvate (105 mg, 1.0 mmol) were successively added, and the mixture was stirred at -78°C for one hr. The temperature of the reaction solution was raised to -40°C, and the reaction solution was stirred for additional one hr. A saturated aqueous ammonium chloride solution was added thereto, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give the title compound (6) (in the structural formula, R³=H, R⁴=CH₃, R⁵=CH₃, and R⁶=CH₃) (166 mg, 59%).

¹H NMR (CDCl₃) δ 0.92-0.96 (d×2, J = 6.9 Hz, 3H), 1.24-1.30 (s×2, 3H), 1.45 (s, 3H), 1.70-1.82 (m, 1H), 1.80 (s, 3H), 1.90-2.74 (m, 7H), 3.70-3.80 (s, 3H), 3.85-4.13 (m, 4H), 4.75 (br s, 1H); MS (ESI) m/z 353(M+H)⁺.

Example B12(4aR*,5R*)-4a,7-Dihydro-3,4a,5,9-tetramethylnaphtho[2,3-b]furan-2,6(4H,5H)-dione

The compound prepared in Example B11 (520 mg, 4.7 mmol) was dissolved in benzene (30 ml), p-toluenesulfonic acid (150 mg, 2.4 mmol) was added to the solution, and the mixture was heated under reflux for 4 hr. The reaction mixture was cooled, and a saturated aqueous sodium bicarbonate solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (173 mg, 45%).

¹H NMR (CDCl₃) δ 0.89 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.93 (s, 3H), 2.04 (s, 3H), 2.52 (d, J = 16.3 Hz, 1H), 2.78

(d, J = 16.3 Hz, 1H), 2.84 (q, J = 6.8 Hz, 1H), 3.03 (dd, J = 23.3, 4.2 Hz, 1H), 3.20 (dd, J = 23.3, 4.2 Hz, 1H), 5.96 (br dd, 1H); MS (ESI) m/z 259(M+H)⁺.

Example B13

(4aR*,5R*,6S*)-6-Hydroxy-4a,5,6,7-tetrahydro-3,4a,5,9-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B12 (170 mg, 0.7 mmol) was dissolved in methanol (5 ml), sodium borohydride (15 mg, 0.6 mmol) was added thereto, and the mixture was stirred at 25°C for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (87 mg, 51%).

¹H NMR (CDCl₃) δ 1.14 (s, 3H), 1.21 (d, J = 7.2 Hz, 3H), 1.77 (dq, J = 7.2, 2.5 Hz, 1H), 1.89 (s, 3H), 2.01 (s, 3H), 2.19 (d, J = 16.1 Hz, 1H), 2.46 (br dd, J = 19.7, 4.2 Hz, 1H), 2.60 (ddd, J = 19.7, 5.0, 3.2 Hz, 1H), 2.81 (d, J = 16.1 Hz, 1H), 4.02 (br s, 1H), 5.89 (br dd, 1H); MS (EI) m/z 260(M)⁺.

Example B14

(4aR*,5R*,6S*)-6-Acetoxy-4a,5,6,7-tetrahydro-3,4a,5,9-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B13 (8.0 mg, 0.03 mmol) was dissolved in methylene chloride (1.0 ml), 4-dimethylaminopyridine (15.0 mg, 0.12 mmol) and acetyl chloride (10.0 mg, 0.15 mmol) were added thereto, and the mixture was stirred at 25°C for 7 hr. Water was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (5.7 mg, 50%).

¹H NMR (CDCl₃) δ 1.10 (d, J = 7.2 Hz, 3H), 1.10 (d, J = 0.8 Hz, 3H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 2.02 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.20 (d, J = 16.7 Hz, 1H), 2.45 (br dd, J = 20.6, 5.0 Hz, 1H), 2.60 (ddd, J = 20.6, 5.0, 3.3 Hz, 1H), 2.83 (d, J = 16.7 Hz, 1H), 5.13 (br d, J = 5.7 Hz, 1H), 5.85 (br dd, 1H); MS (ESI) m/z 303(M+H)⁺.

Example B15

(4aR*,5R*,6S*)-6-Propionyloxy-4a,5,6,7-tetrahydro-3,4a,5,9-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B14, except that the compound prepared in Example B13 was reacted with propionyl chloride.

¹H NMR (CDCl₃) δ 1.10 (d, J = 7.2 Hz, 3H), 1.11 (d, J = 0.6 Hz, 3H), 1.15 (t, J = 7.6 Hz, 3H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 1.90 (s, 3H), 2.01 (s, 3H), 2.21 (d, J = 16.1 Hz, 1H), 2.34 (q, J = 7.6 Hz, 2H), 2.44 (br dd, J = 20.1, 5.1 Hz, 1H), 2.62 (ddd, J = 20.1, 5.4, 3.1 Hz, 1H), 2.83 (d, J = 16.1 Hz, 1H), 5.15 (br dd, 1H), 5.85 (br dd, 1H); MS (ESI) m/z 317(M+H)⁺.

Example B16

(4aR*,5R*,6S*)-6-Benzoyloxy-4a,5,6,7-tetrahydro-3,4a,5,9-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B13 (8.0 mg, 0.03 mmol) was dissolved in pyridine (1.0 ml), benzoyl chloride (25.0 mg, 0.18 mmol) was added thereto, and the mixture was stirred at 25°C for 2.5 hr. A 15% aqueous potassium hydrogensulfate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (5.7 mg, 50%).

¹H NMR (CDCl₃) δ 1.19 (d, J = 7.2 Hz, 3H), 1.27 (d, J = 0.8 Hz, 3H), 1.92 (s, 3H), 2.03 (s, 3H), 2.05 (dq, J = 7.2, 2.5 Hz, 1H), 2.27 (d, J = 16.3 Hz, 1H), 2.60 (br dd, J = 20.5, 4.4 Hz, 1H), 2.75 (ddd, J = 20.5, 5.5, 3.3 Hz, 1H), 2.88 (d, J = 16.3 Hz, 1H), 5.41 (br t, 1H), 5.89 (br t, 1H), 7.43-8.13 (m, 5H); MS (ESI) m/z 365(M+H)⁺.

Example B17(4aR*,5R*,6S*)-6-(2-Furoyl)oxy-4a,5,6,7-tetrahydro-3,4a,5,9-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B16, except that the compound prepared in Example B13 was reacted with 2-furoyl chloride.

¹H NMR (CDCl₃) δ 1.17 (d, J = 6.9 Hz, 3H), 1.23 (s, 3H), 1.92 (s, 3H), 2.01 (dq, J = 7.2, 2.5 Hz, 1H), 2.03 (s, 3H), 2.25 (d, J = 16.2 Hz, 1H), 2.59 (br dd, J = 20.5, 3.7 Hz, 1H), 2.71 (ddd, J = 20.5, 5.4, 3.3 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H), 5.36 (br dd, 1H), 5.87 (br dd, 1H), 6.50 (br dd, J = 3.5, 1.8 Hz, 1H), 7.12 (dd, J = 3.5, 0.8 Hz, 1H), 7.58 (dd, J = 1.5, 0.8 Hz, 1H); MS (ESI) m/z 355 (M+H)⁺.

Example B18(4'S*,6'R*,7'R*)-Spiro[1,3-dioxolane-2,8'-[6',7'-dimethyl-4'-(1"-hydroxy-1"-methoxycarbonyl)propyl]bicyclo[4.4.0]deca-1'-en-3'-one]]

A 2 M solution of lithium diisopropylamide in THF (1.9 ml, 3.8 mmol) was added to anhydrous THF (1 ml) at -78°C under an argon gas stream, a THF solution (2 ml) containing the compound (4) (in the structural formula, R⁵ = H) (420 mg, 1.7 mmol) was added thereto, and the mixture was stirred for one hr. Subsequently, a saturated solution of zinc chloride in THF (2.5 ml) and an anhydrous THF solution (2 ml) containing methyl 2-oxobutyrate (420 mg, 3.6 mmol) were successively added, and the mixture was stirred at -78°C for one hr. The temperature of the reaction solution was raised to -40°C, and the reaction solution was stirred for additional one hr. A saturated aqueous ammonium chloride solution was added thereto, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give the title compound (6) (in the structural formula, R³=H, R⁴=CH₂CH₂, R⁵=H, and R⁶=CH₃) (290 mg, 46%).

¹H NMR (CDCl₃) δ 0.95 (d, J = 6.7 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H), 1.27 (s, 3H), 1.81 (dq, J = 7.4, 2.5 Hz, 1H), 1.83 (q, J = 7.4 Hz, 2H), 1.90-2.74 (m, 7H), 3.73 (s, 3H), 3.80-4.09 (m, 4H), 4.62 (s, 1H), 5.73 (d, J = 1.7 Hz, 1H); MS (SIMS) m/z 353(M+H)⁺.

Example B19(4aR*,5R*)-4a,7-Dihydro-3-ethyl-4a,5-dimethylnaphtho[2,3-b]furan-2,6(4H,5H)-dione

The compound prepared in Example B18 (290 mg, 0.8 mmol) was dissolved in benzene (20 ml), p-toluenesulfonic acid (90 mg, 0.3 mmol) was added to the solution, and the mixture was heated under reflux for 2 hr. The reaction mixture was cooled, diluted with ethyl acetate (20 ml), washed with a saturated aqueous sodium bicarbonate solution and saturated saline in that order, and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (163 mg, 77%).

¹H NMR (CDCl₃) δ 0.92 (s, 3H), 1.15 (t, J = 7.7 Hz, 3H), 1.15 (d, J = 7.6 Hz, 3H), 2.39 (m, 2H), 2.55 (d, J = 16.4 Hz, 1H), 2.81 (q, J = 7.6 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H), 3.02 (dd, J = 23.4, 3.9 Hz, 1H), 3.16 (dd, J = 23.6, 4.1 Hz, 1H), 5.84 (m, 1H), 6.03 (s, 1H).

Example B20(4aR*,5R*,6S*)-4a,5-Dimethyl-3-ethyl-6-hydroxy-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B19 (163 mg, 0.6 mmol) was dissolved in methanol (5.0 ml), sodium borohydride (6.0 mg, 0.19 mmol) was added thereto, and the mixture was stirred at 25°C for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (78 mg, 48%).

¹H NMR (CDCl₃) δ 1.13 (t, J = 7.6 Hz, 3H), 1.18 (d, J = 0.8 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.75 (dq, J = 7.2, 2.5 Hz, 1H), 2.21 (d, J = 16.3 Hz, 1H), 2.34, 2.36 (each br dq, J = 7.6 Hz, 2H), 2.40 (br dd, 1H), 2.59 (m, 1H), 2.86 (d, J = 16.3 Hz, 1H), 4.03 (br s, 1H), 5.76 (br t, 1H), 5.99 (s, 1H); MS (ESI) m/z 261(M+H)⁺.

Example B21(4aR*,5R*,6S*)-6-Acetoxy-4a,5-dimethyl-3-ethyl-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B20 (10.0 mg, 0.04 mmol) was dissolved in methylene chloride (1.0 ml), 4-dimethylaminopyridine (15.0 mg, 0.12 mmol) and acetyl chloride (12.0 mg, 0.20 mmol) were added thereto, and the mixture was stirred at 25°C for 20 hr. Water was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (9.1 mg, 78%).

¹H NMR (CDCl₃) δ 1.10 (d, J = 7.2 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H), 1.15 (s, 3H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 2.06 (s, 3H), 2.23 (d, J = 16.1 Hz, 1H), 2.33-2.39 (m, 1H), 2.35, 2.37 (each br dq, J = 7.6 Hz, 2H), 2.59 (ddd, J = 20.5, 7.5, 3.1 Hz, 1H), 2.88 (d, J = 16.1 Hz, 1H), 5.14 (m, 1H), 5.72 (br t, 1H), 5.98 (s, 1H); MS (ESI) m/z 303 (M+H)⁺.

Example B22(4aR*,5R*,6S*)-4a,5-Dimethyl-3-ethyl-6-propionyloxy-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B21, except that the compound prepared in Example B20 was reacted with propionyl chloride.

¹H NMR (CDCl₃) δ 1.10 (d, J = 7.2 Hz, 3H), 1.13 (t, J = 7.7 Hz, 3H), 1.14 (t, J = 7.7 Hz, 3H), 1.15 (s, 3H), 1.91 (dq, J = 7.2, 2.6 Hz, 1H), 2.34 (d, J = 16.2 Hz, 1H), 2.35-2.36 (m, 4H), 2.40 (br dd, 1H), 2.57-2.64 (m, 1H), 2.88 (d, J = 16.2 Hz, 1H), 5.15-5.17 (m, 1H), 5.72 (br t, 1H), 5.99 (s, 1H); MS (ESI) m/z 317 (M+H)⁺.

Example B23(4aR*,5R*,6S*)-6-Benzoyloxy-4a,5-dimethyl-3-ethyl-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B20 (10.0 mg, 0.04 mmol) was dissolved in pyridine (1.0 ml), benzoyl chloride (16.0 mg, 0.12 mmol) was added thereto, and the mixture was stirred at 25°C for 2 hr. A 15% aqueous potassium hydrogensulfate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (4.7 mg, 34%).

¹H NMR (CDCl₃) δ 1.16 (t, J = 7.8 Hz, 3H), 1.19 (d, J = 7.5 Hz, 3H), 1.32 (s, 3H), 2.05 (dq, J = 7.5, 2.5 Hz, 1H), 2.31 (d, J = 16.1 Hz, 1H), 2.37, 2.39 (each br q, J = 7.8 Hz, 2H), 2.56 (br dd, J = 20.8, 5.3 Hz, 1H), 2.73 (br ddd, 1H), 2.94 (d, J = 16.1 Hz, 1H), 5.43 (br t, 1H), 5.77 (br t, 1H), 6.02 (s, 1H), 7.43-8.06 (m, 5H); MS (ESI) m/z 365 (M+H)⁺.

Example B24(4aR*,5R*,6S*)-4a,5-Dimethyl-3-ethyl-6-(2-furoyl)oxy-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B23, except that the compound prepared in Example B20 was reacted with 2-furoyl chloride.

¹H NMR (CDCl₃) δ 1.14 (t, J = 7.5 Hz, 3H), 1.16 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H), 2.00 (dq, J = 7.2, 2.5 Hz, 1H), 2.28 (d, J = 16.1 Hz, 1H), 2.37, 2.38 (each br q, J = 7.5 Hz, 2H), 2.54 (dd, J = 21.0, 5.2 Hz, 1H), 2.69 (br dd, 1H), 2.92 (d, J = 16.1 Hz, 1H), 5.38 (br s, 1H), 5.75 (t, J = 3.9 Hz, 1H), 6.01 (s, 1H), 6.50 (dd, J = 3.6, 0.8 Hz, 1H), 7.12 (d, J = 3.6 Hz, 1H), 7.58 (t, J = 0.8 Hz, 1H); MS (ESI) m/z 355 (M+H)⁺.

Example B25(4'S*,6'R*,7'R*)-Spiro[1,3-dioxolane-2,8']-[6',7'-dimethyl-4'-(1"-hydroxy-1"-methoxycarbonyl)methylbicyclo[4.4.0]deca-1'-ene-3'-one]

The compound (4) (in the structural formula, R⁵ = H) (800 mg, 3.4 mmol) was dissolved in ethanol (10 ml), a 1 N aqueous sodium hydroxide solution (30 ml, 3 mmol) was added to the solution, and a previously prepared 1.2 M aqueous glyoxalic acid solution (10 ml, 12 mmol) was added thereto, and the mixture was stirred at 50°C for 3 hr. The reaction solution was diluted with water, washed with ethyl acetate, and the water layer was adjusted to pH 2.5 and then

extracted with methylene chloride. On the other hand, the organic layer was dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixed solution of benzene (12 ml) and methanol (4 ml), and a 2 M solution of trimethylsilyldiazomethane in hexane (2.5 ml, 5 mmol) was dropwise added thereto at 25°C. The solvent was then removed by distillation under reduced pressure to give the title compound (6) (in the structural formula, R³ = H, R⁴ = H, R⁵ = H, and R⁶ = CH₃).

¹H NMR (CDCl₃) δ 0.85-0.93 (d×2, J = 6.9 Hz, 3H), 1.26-1.31 (s×2, 3H), 1.51-1.59 (dt ×2, 1H), 1.74 (dd, J = 13.0, 4.7 Hz, 1H), 1.79 (d, J = 6.9 Hz, 1H), 1.93 (br t, 2H), 2.22-2.30 (m, 1H), 2.58-2.68 (m, 1H), 2.80-2.94 (m, 2H), 3.82 (s×2, 3H), 3.84-4.13 (m, 4H), 4.94-4.96 (m, 1H), 5.80-5.81 (s×2, 1H); MS (ESI) m/z 325(M+H)⁺.

10 Example B26

(4aR*,5R*,6S*)-4a,5-Dimethyl-6-hydroxy-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B25 (450 mg) was dissolved in benzene (10 ml), p-toluenesulfonic acid (20 mg, 0.10 mmol) was added to the solution, and the mixture was stirred at 60°C for one hr. The reaction mixture was cooled, and a saturated aqueous sodium bicarbonate solution was added thereto, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in methanol (6 ml), sodium borohydride (40 mg, 1.3 mmol) was added thereto, and the mixture was stirred at 25°C for 10 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1) to give the title compound (39.8 mg, 5%).

¹H NMR (CDCl₃) δ 1.19 (d, J = 7.3 Hz, 3H), 1.21 (s, 3H), 1.75 (dq, J = 7.3, 2.5 Hz, 1H), 2.34 (br d, J = 16.4 Hz, 1H), 2.44 (br dd, J = 20.8, 5.3 Hz, 1H), 2.60 (ddd, J = 20.8, 7.3, 3.6 Hz, 1H), 2.94 (d, J = 16.4 Hz, 1H), 4.04 (br s, 1H), 5.83 (br s×2, 2H), 6.09 (s, 1H); MS (ESI) m/z 233(M+H)⁺.

Example B27

(4aR*,5R*,6S*)-6-Acetoxy-4a,5-dimethyl-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B26 (8.0 mg, 0.03 mmol) was dissolved in methylene chloride (1.0 ml), 4-dimethylaminopyridine (15.0 mg, 0.12 mmol) and acetyl chloride (10.0 mg, 0.15 mmol) were added thereto, and the mixture was stirred at 25°C for 7 hr. Water was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 3 : 1) to give the title compound (1.97 mg, 21%).

¹H NMR (CDCl₃) δ 1.08 (d, J = 7.2 Hz, 3H), 1.18 (d, J = 0.8 Hz, 3H), 1.90 (dq, J = 7.2, 2.5 Hz, 1H), 2.07 (s, 3H), 2.36 (d, J = 16.5 Hz, 1H), 2.43 (br dd, J = 20.9, 4.6 Hz, 1H), 2.60 (ddd, J = 20.9, 8.99, 4.6 Hz, 1H), 2.96 (d, J = 16.5 Hz, 1H), 5.14 (br t, 1H), 5.19 (br t, 1H), 5.86 (s, 1H), 6.08 (s, 1H); MS (ESI) m/z 275(M+H)⁺.

Example B28

(4aR*,5R*,6S*)-4a,5-Dimethyl-6-propyloxy-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B27, except that the compound prepared in Example B26 was reacted with propionyl chloride.

¹H NMR (CDCl₃) δ 1.08 (d, J = 7.2 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H), 1.18 (s, 3H), 1.93 (dq, J = 7.2, 2.5 Hz, 1H), 2.34 (q, J = 7.5 Hz, 2H), 2.35-2.45 (m, 2H), 2.59-2.63 (m, 1H), 2.96 (d, J = 16.6 Hz, 1H), 5.17 (br t, 1H), 5.79 (br t, 1H), 5.86 (s, 1H), 6.08 (s, 1H); MS (FAB) m/z 289(M+H)⁺.

Example B29

(4aR*,5R*,6S*)-6-Benzoyloxy-4a,5-dimethyl-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B26 (8.0 mg, 0.03 mmol) was dissolved in pyridine (1.0 ml), benzoyl chloride (20.0 mg, 0.15 mmol) was added thereto, and the mixture was stirred at 25°C for 2 hr. A 15% aqueous potassium hydrogensulfate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was

washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 3 : 1) to give the title compound (3.0 mg, 30%).

¹H NMR (CDCl₃) δ 1.16 (d, J = 7.2 Hz, 3H), 1.34 (s, 3H), 2.05 (dq, J = 7.2, 2.5 Hz, 1H), 2.43 (d, J = 16.6 Hz, 1H), 2.57 (br dd, J = 21.0, 4.7 Hz, 1H), 2.75 (ddd, J = 21.0, 5.3, 3.2 Hz, 1H), 3.02 (d, J = 16.6 Hz, 1H), 5.43 (br d, J = 3.2 Hz, 1H), 5.83 (br t, 1H), 5.89 (s, 1H), 6.12 (s, 1H), 7.43-8.05 (m, 5H); MS (EIS) m/z 337(M+H)⁺.

Example B30

10 (4aR*,5R*,6S*)-4a,5-Dimethyl-6-(2-furoyl)oxy-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B29, except that the compound prepared in Example B26 was reacted with 2-furoyl chloride.

¹H NMR (CDCl₃) δ 1.14 (d, J = 7.2 Hz, 3H), 1.30 (s, 3H), 2.00 (dq, J = 7.2, 2.5 Hz, 1H), 2.40 (br d, J = 16.7 Hz, 1H), 2.56 (dd, J = 21.4, 4.9 Hz, 1H), 2.69 (br ddd, J = 21.4, 8.1, 3.6 Hz, 1H), 3.00 (d, J = 16.7 Hz, 1H), 5.38 (br d, J = 5.6 Hz, 1H), 5.82 (br t, 1H), 5.88 (s, 1H), 6.11 (s, 1H), 6.51 (dd, J = 3.6, 1.8 Hz, 1H), 7.12 (dd, J = 3.6, 0.8 Hz, 1H), 7.58 (dd, J = 1.8, 0.8 Hz, 1H); MS (ESI) m/z 327(M+H)⁺.

Example B31

20 (5'S*,6'R*,7'R*)-Spiro[1,3-dioxolane-2,8'-(5',6',7'-trimethylbicyclo[4,4,0]deca-1'-ene-3'-one)]

The compound (4) (in the structural formula, R⁵ = H) (500 mg, 2.1 mmol) was dissolved in toluene (30 ml), DDQ (700 mg, 3.1 mmol) was added thereto, and the mixture was heated under reflux for 10 hr. The reaction solution was cooled, and the resultant precipitate was filtered, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give a Δ^{1,4}-dienone form (490 mg, 98%).

Cuprous iodide (1.5 g, 8 mmol) was added to anhydrous diethyl ether (15 ml) under an argon gas stream, and the mixture was cooled to 0°C. A 1.0 M methylolithium diethyl ether solution (16 ml, 16 mmol) was added thereto, and the mixture was stirred for 15 min. A solution of the above compound (890 mg, 3.8 mmol) in diethyl ether (10 ml) was added to the reaction solution, and the mixture was stirred for 15 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give the title compound (5) (in the structural formula, R³ = CH₃ and R⁵ = H) (594 mg, 63%).

¹H NMR (CDCl₃) δ 0.90 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.35 (s, 3H), 1.54 (ddd, J = 17.8, 13.3, 4.4 Hz, 1H), 1.92 (ddd, J = 13.3, 5.0, 3.0 Hz, 1H), 2.10 (q, J = 6.9 Hz, 1H), 2.10 - 2.20 (m, 2H), 2.28 (ddd, J = 15.0, 4.2, 2.7 Hz, 1H), 2.63 (dddd, J = 17.8, 15.0, 4.2, 2.7 Hz, 1H), 2.77 (dd, 1H), 3.84 - 4.11 (m, 4H), 5.75 (s, 1H); MS (EI) m/z 250 (M)⁺.

40 Example B32

(4'S*,5'S,6'R*,7'R*)-Spiro[1,3-dioxolane-2,8'-(4'-(1"-hydroxy-1"-methoxycarbonyl)ethyl-5',6',7'-trimethylbicyclo[4,4,0]deca-1'-en-3'-one)]

A 2 M solution of lithium diisopropylamide in THF (3.5 ml, 17.5 mmol) was added to anhydrous THF (5 ml) at -78°C under an argon gas stream, a THF solution (10 ml) containing the compound prepared in Example B31 (690 mg, 2.8 mmol) was added thereto, and the mixture was stirred for one hr. Subsequently, a saturated solution of zinc chloride in THF (3.5 ml) and an anhydrous THF solution containing methyl pyruvate (850 mg, 8.3 mmol) were successively added, and the mixture was stirred at -78°C for one hr. A saturated aqueous ammonium chloride solution was added thereto, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (6) (in the structural formula, R³ = CH₃, R⁴ = CH₃, R⁵ = H, and R⁶ = CH₃) (763 mg, 78%).

¹H NMR (CDCl₃) δ 0.85-0.96 (d×2, J = 6.8 Hz, 3H), 1.02-1.11 (d×2, J = 7.2 Hz, 3H), 1.44 (s×2, 3H), 1.55-1.63 (m, 2H), 1.86-1.91 (m, 1H), 2.15 (q, J = 6.8 Hz, 1H), 2.27-2.38 (m, 2H), 2.58-2.67 (m, 1H), 3.74-4.13 (m, 7H), 5.79 (s×2, 1H); MS (FAB) m/z 353 (M+H)⁺.

Example B33(4R*,4aR*,5R*)-4a,7-Dihydro-3,4,4a,5-tetramethylnaphtho[2,3-b]furan-2,6(4H,5H)-dione

5 The compound prepared in Example B32 (760 mg, 2.2 mmol) was dissolved in benzene (30 ml), p-toluenesulfonic acid (300 mg, 1.8 mmol) was added to the solution, and the mixture was heated under reflux for 4 hr. The reaction mixture was cooled, and a saturated aqueous sodium bicarbonate solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel
 10 (hexane : ethyl acetate = 4 : 1) to give the title compound (460 mg, 85%).

¹H NMR (CDCl₃) δ 0.90 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H), 1.95 (s, 3H), 2.80 (q, J = 7.2 Hz, 1H), 2.95 (q, J = 6.7 Hz, 1H), 2.99 (br dd, J = 22.8, 3.8 Hz, 1H), 3.20 (dd, J = 22.8, 3.8 Hz, 1H), 5.91 (m, 1H), 5.98 (s, 1H); MS (EI) m/z 258 (M)⁺.

15 Example B34(4R*,4aR*,5R*,6S*)-6-Hydroxy-4a,5,6,7-tetrahydro-3,4,4a,5-tetramethylnaphtho[2,3-b]furan-2(4H)-one

20 The compound prepared in Example B33 (600 mg, 2.1 mmol) was dissolved in methanol (150 ml), sodium borohydride (45 mg, 1.8 mmol) was added thereto, and the mixture was stirred at 25°C for 30 min. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (310 mg, 51%).

25 ¹H NMR (CDCl₃) δ 0.94 (d, J = 7.5 Hz, 3H), 1.13 (s, 3H), 1.14 (d, J = 7.2 Hz, 3H), 1.93 (s, 3H), 1.95 (dq, J = 7.5, 2.0 Hz, 1H), 2.40 (br dd, J = 19.8, 5.4 Hz, 1H), 2.60 (br ddd, J = 19.8, 5.4, 3.8 Hz, 1H), 2.82 (q, J = 7.2 Hz, 1H), 4.09 (br s, 1H), 5.88 (m, 1H), 5.95 (s, 1H); MS (EI) m/z 260 (M)⁺.

Example B35

30

(4R*,4aR*,5R*,6S*)-6-Acetoxy-4a,5,6,7-tetrahydro-3,4,4a,5-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B34 (10 mg, 0.04 mmol) was dissolved in methylene chloride (1.0 ml), 4-dimethylaminopyridine (15.0 mg, 0.12 mmol) and acetyl chloride (20.0 mg, 0.3 mmol) were added thereto, and the mixture was stirred at 25°C for 7 hr. Water was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (5.7 mg, 50%).

40 ¹H NMR (CDCl₃) δ 0.95 (d, J = 7.1 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H), 1.60 (s, 3H), 1.93 (s, 3H), 2.06 (s, 3H), 2.11 (dq, J = 7.2, 2.5 Hz, 1H), 2.40 (br dd, J = 20.6, 5.3 Hz, 1H), 2.60 (br ddd, J = 20.6, 5.3, 3.8 Hz, 1H), 2.84 (q, J = 7.2 Hz, 1H), 5.18 (m, 1H), 5.84 (m, 1H), 5.94 (s, 1H); MS (ESI) m/z 303 (M+H)⁺.

Example B3645 (4R*,4aR*,5R*,6S*)-6-Propionyloxy-4a,5,6,7-tetrahydro-3,4,4a,5-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B35, except that the compound prepared in Example B34 was reacted with propionyl chloride.

50 ¹H NMR (CDCl₃) δ 0.95 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 7.2 Hz, 3H), 1.16 (t, J = 7.4 Hz, 3H), 1.93 (s, 3H), 2.12 (dq, J = 7.2, 2.8 Hz, 1H), 2.34 (q, J = 7.4 Hz, 2H), 2.38 (br dd, J = 19.3, 5.5 Hz, 1H), 2.60 (br ddd, J = 19.3, 5.5, 3.8 Hz, 1H), 2.84 (q, J = 7.4 Hz, 1H), 5.20 (m, 1H), 5.83 (m, 1H), 5.94 (s, 1H); MS (ESI) m/z 317 (M+H)⁺.

Example B3755 (4R*,4aR*,5R*,6S*)-6-Benzoyloxy-4a,5,6,7-tetrahydro-3,4,4a,5-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B34 (10 mg, 0.04 mmol) was dissolved in pyridine (1.0 ml), benzoyl chloride (25.0 mg, 0.18 mmol) was added thereto, and the mixture was stirred at 25°C for 2.5 hr. A 15% aqueous potassium

EP 0 885 893 A1

hydrogensulfate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (5.7 mg, 50%).

¹H NMR (CDCl₃) δ 0.99 (d, J = 7.2 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 1.32 (s, 3H), 1.95 (s, 3H), 2.24 (dq, J = 7.2, 2.5 Hz, 1H), 2.55 (br dd, J = 20.8, 5.1 Hz, 1H), 2.69-2.76 (m, 1H), 2.88 (q, J = 7.2 Hz, 1H), 5.46 (m, 1H), 5.87 (m, 1H), 5.97 (s, 1H), 7.42-7.99 (m, 5H); MS (FAB) m/z 365 (M+H)⁺.

Example B38

(4R*,4aR*,5R*,6S*)-6-(2-Furoyl)oxy-4a,5,6,7-tetrahydro-3,4,4a,5-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B37, except that the compound prepared in Example B34 was reacted with 2-furoyl chloride.

¹H NMR (CDCl₃) δ 0.98 (d, J = 7.2 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.95 (s, 3H), 2.20 (dq, J = 7.2, 2.5 Hz, 1H), 2.53 (br dd, J = 20.8, 5.0 Hz, 1H), 2.69 (br ddd, J = 20.8, 5.0, 3.8 Hz, 1H), 2.87 (q, J = 7.2 Hz, 1H), 5.41 (m, 1H), 5.86 (m, 1H), 5.96 (s, 1H), 6.50 (dd, J = 3.6, 1.8 Hz, 1H), 7.11 (dd, J = 3.6, 0.8 Hz, 1H), 7.58 (dd, J = 1.8, 0.8 Hz, 1H); MS (ESI) m/z 355 (M+H)⁺.

Example 39

(4aR*,5R*,6R*,7S*)-6,7-Dihydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B1 (5 mg, 0.02 mmol) was dissolved in dioxane (1 ml), selenium dioxide (22 mg, 0.20 mmol) was added thereto, and the mixture was stirred at 50°C for 2 days. The reaction solution was filtered, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to give the title compound (4.5 mg, 86%).

Reference Example 2

(4aR*,5R*,6R*,7S*)-6-Hydroxy-7-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B39 (15 mg, 0.06 mmol) was dissolved in methylene chloride (0.3 ml), diisopropylethylamine (25 µl, 0.14 mmol) and propionyl chloride (12 mg, 0.13 mmol) were added to the solution under ice cooling, and the mixture was stirred under ice cooling for 30 min and then at 25°C for 17 hr. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and then with a saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent was then removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to give the title compound (8.2 mg, 45%).

Reference Example 3

(4aR*,5R*,6R*,7S*)-7-Hydroxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B39 (9.9 mg, 0.04 mmol) was dissolved in methylene chloride (0.2 ml), 4-dimethylaminopyridine (4.5 mg, 0.04 mmol) and propionyl chloride (9 mg, 0.09 mmol) were added to the solution under ice cooling, and the mixture was stirred under ice cooling for 30 min and then at 25°C for 22 hr. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and then with a saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent was then removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to give the title compound (4.9 mg, 41%).

Reference Example 4

(4aR*,5R*,6R*,7S*)-6,7-Dipropionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B39 (16 mg, 0.06 mmol) was dissolved in methylene chloride (0.35 ml), 4-dimethylaminopyridine (38 mg, 0.31 mmol) and propionyl chloride (24 µl, 0.28 mmol) were added to the solution under

EP 0 885 893 A1

ice cooling, and the mixture was stirred under ice cooling for 30 min and then at 25°C for 18 hr. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a 5% aqueous potassium hydrogensulfate solution and then with a saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent was then removed by distillation under reduced pressure. The residue was purified by preparative TLC (toluene : ethyl acetate = 5 : 1) to give the title compound (20 mg, 85%).

Example B40

(4aR*,5R*,6R*,7S*)-6,7-Dihydroxy-4a,5,6,7-tetrahydro-3,4a,5,9-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B39, except that the compound prepared in Example B13 was reacted with selenium dioxide.

¹H NMR (CDCl₃) δ 1.17 (s, 3H), 1.25 (d, J = 7.2 Hz, 3H), 1.80 (dq, J = 7.2, 1.5 Hz, 1H), 1.90 (s, 3H), 2.03 (s, 3H), 2.17 (d, J = 16.4 Hz, 1H), 2.25-2.37 (m, 2H), 2.83 (d, J = 16.4 Hz, 1H), 3.93 (br s, 1H), 4.40 (br s, 1H), 5.76 (s, 1H); MS (ESI) m/z = 277(M+H)⁺.

Example B41

(4aR*,5R*,6R*,7S*)-6,7-Dihydroxy-4a,5-dimethyl-3-ethyl-4a,5,6,7-tetrahydronaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B39, except that the compound prepared in Example B20 was reacted with selenium dioxide.

¹H NMR (CDCl₃) δ 1.13 (t, J = 7.5 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H), 1.26 (d, J = 2.7 Hz, 3H), 1.80 (dq, J = 7.2, 1.5 Hz, 1H), 2.20 (d, J = 16.1 Hz, 1H), 2.30-2.40 (m, 2H), 2.87 (d, J = 16.1 Hz, 1H), 3.94 (br s, 1H), 4.37 (br s, 1H), 5.65 (s, 1H), 5.98 (s, 1H); MS (ESI) m/z = 276(M)⁺.

Example B42

The compound prepared in Example B2 was dissolved in ethanol and adjusted to a concentration of 0.5 mg/ml. This sample was chromatographed using an optical resolution column (CHIRALPAK AS) by elution with a mobile phase (hexane : isopropyl alcohol = 9 : 1) to give optical isomers.

Angle of rotation: front peak: +10.2° (nonnatural type) rear peak: -10.2° (natural type)

Example B43

(6'R*,7'R*)-Spiro[1,3-dioxolane-2,3'-(6',7'-dimethylbicyclo[4.4.0]-deca-1'-en-8'-one)]

Compound (4) (in the structural formula, R⁵ = H) (1 g, 4.24 mmol) was dissolved in methylene chloride (50 ml), and the solution was cooled to 0°C. A 60% aqueous perchloric solution (1 ml) was added to the solution, and the mixture was stirred at that temperature for one hr and then at room temperature for 20 min. A saturated aqueous sodium bicarbonate solution (25 ml) was added to the reaction solution, followed by separation. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give a corresponding diketone form (797 mg, 78%). The above compound (790 mg, 4.11 mmol) was dissolved in anhydrous methylene chloride (5 ml) under an argon gas stream, trimethylsilyl trifluoromethanesulfonate (17 μl, 0.02 mmol) and 1,2-bis(trimethylsilyloxy)ethane (1.2 ml, 4.3 mmol) were added to the solution at -78°C, and the mixture was stirred at that temperature for 4 days. An excess of pyridine was added to the reaction solution, the temperature of the mixture was raised to 25°C, a saturated aqueous ammonium chloride solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give the title compound (730 mg, 75%).

¹H NMR (CDCl₃) δ 0.92 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.64 - 1.86 (m, 4H), 2.47 - 2.50 (m, 4H), 2.56 - 2.68 (m, 1H), 3.92 - 4.08 (m, 4H), 5.47 (s, 1H); MS (ESI) m/z 237 (M+H)⁺.

Example B44(6R*,7S*,8S*,9R*)-8-Hydroxy-6,7,9-trimethylbicyclo[4.4.0]deca-1-en-3-one

A 2 M solution of lithium diisopropylamide in THF (2.0 ml, 4.0 mmol) were added to anhydrous THF (2 ml) at -78°C under an argon gas stream, a THF solution (5 ml) containing the compound (8) (in the structural formula, R³ = H and R⁵ = H) (730 mg, 3.8 mmol) was added thereto, and the mixture was stirred for one hr. Methyl iodide (1.4 mg, 10 mmol) was added thereto, the temperature was raised to 25°C, and the mixture was stirred for one hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate. The solvent was removed by distillation under reduced pressure. The resultant crude product was dissolved in THF (10 ml), lithium borohydride (30 mg, 1.4 mmol) was added thereto, and the mixture was stirred at 25°C for 14 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. Subsequently, the resultant crude product was dissolved in acetone (10 ml), p-toluenesulfonic acid (20 mg, 0.1 mmol) was added thereto, and the mixture was stirred at 25°C for 20 min. A saturated sodium bicarbonate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (250 mg, 40%).

¹H NMR (CDCl₃) δ 0.91 (d, J = 7.3 Hz, 3H), 1.08 (d, J = 7.3 Hz, 3H), 1.31 (s, 3H), 1.64 (dq, J = 7.3, 2.9 Hz, 1H), 1.61 - 1.73 (m, 2H), 1.93 (br d, J = 13.9 Hz, 1H), 2.03 (ddd, J = 13.9, 5.1, 2.9 Hz, 1H), 2.12 - 2.20 (m, 1H), 2.29 - 2.35 (m, 1H), 2.45 (dd, J = 14.6, 5.1 Hz, 1H), 3.04 (ddd, J = 14.6, 3.6, 1.7 Hz, 1H), 3.61 (s, 1H), 5.79 (s, 1H); MS (ESI) m/z 209 (M+H)⁺.

Example B45(4S*,6R*,7R*,8S*,9R*)-4-(1'-Hydroxy-1'-methoxycarbonyl)ethyl-8-[(2-methoxyethoxy)methoxy]-6,7,9-trimethylbicyclo[4.4.0]deca-1-en-3-one

Compound (9) (in the structural formula, R¹ = CH₃, R³ = H, and R⁵ = H) (245 mg, 1.18 mmol) was dissolved in methylene chloride (8 ml), diisopropylethylamine (300 mg, 2.36 mmol) and β-methoxyethoxymethyl chloride (300 mg, 2.36 mmol) were added thereto, and the mixture was stirred at 25°C for 14 hr. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give a corresponding MEM form (307 mg, 88%). A 2 M solution of lithium diisopropylamide in THF (0.5 ml, 1.0 mmol) was added to anhydrous THF (2 ml) at -78°C under an argon gas stream, a THF solution (4 ml) containing the compound prepared just above (307 mg, 1.0 mmol) was added thereto, and the mixture was stirred for one hr. Subsequently, a saturated solution of zinc chloride in THF (0.3 ml) and a THF solution (2 ml) containing methyl pyruvate (150 mg, 1.5 mmol) were successively added, and the mixture was stirred at -78°C for 20 min. A saturated aqueous ammonium chloride solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (310 mg, 75%).

¹H NMR (CDCl₃) δ 0.86(d × 2, J = 7.0 Hz, 3H), 1.04 - 1.08(d × 2, J = 7.2 Hz, 3H), 1.30 (s, 3H), 1.32 - 1.34 (s × 2, 3H), 1.67 - 1.79 (m, 2H), 1.90 - 2.19 (m, 2H), 2.28 - 2.31 (m, 1H), 2.71 - 3.03 (dd × 3, J = 14.0, 5.1 Hz, 2H), 3.36 - 3.40 (s × 2, 3H), 3.45 (br s, 1H), 3.71 - 3.79 (s × 2, 3H), 3.56 - 3.83 (m, 4H), 4.71 - 4.84 (d × 2, J = 7.1 Hz, 2H), 5.73 - 5.75 (s × 2, 1H); MS (ESI) m/z 399 (M+H)⁺.

Example B46(4aR*,5R*,6S*,7R*)-6-Hydroxy-4a,5,6,7-tetrahydro-3,4a,5,7-tetramethylnaphtho[2,3-b]furan-2(4H)-one

Compound (10) (in the structural formula, R¹ = CH₃, R³ = H, R⁴ = CH₃, R⁵ = H, and P¹ ≈ MEM) (310 mg, 0.78 mmol) was dissolved in benzene (10 ml), p-toluenesulfonic acid (80 mg, 0.42 mmol) was added to the solution, and the mixture was heated under reflux for 30 min. The reaction solution was cooled, a saturated aqueous sodium bicarbonate solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated

EP 0 885 893 A1

saline and dried over magnesium sulfate, and the solvent was then removed by distillation under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (60 mg, 30%).

¹H NMR (CDCl₃) δ 0.98 (d, J = 7.6 Hz, 3H), 1.10 (s, 3H), 1.14 (d, J = 7.3 Hz, 3H), 1.72 (dq, J = 7.3, 2.4 Hz, 1H), 1.84 (s, 3H), 2.10 (br d, J = 16.1 Hz, 1H), 2.41 (m, 1H), 2.77 (d, J = 16.1 Hz, 1H), 3.62 (br s, 1H), 5.67 (d, J = 4.6 Hz, 1H), 5.91 (s, 1H); MS (ESI) m/z 261 (M+H)⁺.

Example B47

(4aR*,5R*,6S*,7R*)-6-Acetoxy-4a,5,6,7-tetrahydro-3,4a,5,7-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B46 (8 mg, 0.03 mmol) was dissolved in methylene chloride (1.0 ml), 4-dimethylaminopyridine (15 mg, 0.12 mmol) and acetyl chloride (20.0 mg, 0.3 mmol) were added thereto, and the mixture was stirred at 25°C for 14 hr. Water was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (5.1 g, 55%).

¹H NMR (CDCl₃) δ 1.10 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 7.3 Hz, 3H), 1.15 (s, 3H), 1.92 (s, 3H), 1.92 (dq, J = 7.3, 2.7 Hz, 1H), 2.06 (s, 3H), 2.20 (br d, J = 16.1 Hz, 1H), 2.44 (m, 1H), 2.86 (d, J = 16.1 Hz, 1H), 4.81 (m, 1H), 5.69 (d, J = 4.6 Hz, 1H), 5.97 (s, 1H); MS (ESI) m/z 303 (M+H)⁺.

Example B48

(4aR*,5R*,6S*,7R*)-6-Propionyloxy-4a,5,6,7-tetrahydro-3,4a,5,7-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B47, except that the compound prepared in Example B46 was reacted with propionyl chloride.

¹H NMR (CDCl₃) δ 1.09 (d, J = 7.5 Hz, 3H), 1.12 (d, J = 8.0 Hz, 3H), 1.14 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H), 1.92 (s, 3H), 1.94 (dq, J = 7.8, 2.7 Hz, 1H), 2.02 (d, J = 16.8 Hz, 1H), 2.34 (q, J = 7.5 Hz, 2H), 2.42 (m, 1H), 2.85 (d, J = 16.8 Hz, 1H), 4.81 (m, 1H), 5.69 (d, J = 4.6 Hz, 1H), 5.96 (s, 1H); MS (ESI) m/z 317 (M+H)⁺.

Example B49

(4aR*,5R*,6S*,7R*)-6-Benzoyloxy-4a,5,6,7-tetrahydro-3,4a,5,7-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The compound prepared in Example B46 (10 mg, 0.04 mmol) was dissolved in pyridine (1.0 ml), benzoyl chloride (25.0 mg, 0.18 mmol) was added thereto, and the mixture was stirred at 25°C for 2.5 hr. A 15% aqueous potassium hydrogensulfate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated saline and dried over magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was purified by preparative TLC (hexane : ethyl acetate = 4 : 1) to give the title compound (4.0 mg, 35%).

¹H NMR (CDCl₃) δ 1.18 (d, J = 7.1 Hz, 3H), 1.20 (d, J = 7.6 Hz, 3H), 1.31 (s, 3H), 1.94 (s, 3H), 2.07 (dq, J = 7.1, 2.9 Hz, 1H), 2.27 (br d, J = 16.1 Hz, 1H), 2.60 (br dq, J = 7.1, 4.4 Hz, 1H), 2.91 (d, J = 16.1 Hz, 1H), 5.07 (m, 1H), 5.73 (d, J = 4.4 Hz, 1H), 6.00 (s, 1H), 7.42 - 8.12 (m, 5H); MS (ESI) m/z 365 (M+H)⁺.

Example B50

(4aR*,5R*,6S*,7R*)-6-(2-Furoyl)oxy-4a,5,6,7-tetrahydro-3,4a,5,7-tetramethylnaphtho[2,3-b]furan-2(4H)-one

The title compound was prepared in the same manner as in Example B49, except that the compound prepared in Example B46 was reacted with 2-furoyl chloride.

¹H NMR (CDCl₃) δ 1.16 (d, J = 7.1 Hz, 3H), 1.17 (d, J = 7.3 Hz, 3H), 1.26 (s, 3H), 1.93 (s, 3H), 2.02 (dq, J = 7.3, 2.7 Hz, 1H), 2.24 (br d, J = 16.1 Hz, 1H), 2.57 (br dq, J = 7.3, 4.6 Hz, 1H), 2.89 (d, J = 16.1 Hz, 1H), 5.04 (m, 1H), 5.72 (d, J = 4.6 Hz, 1H), 5.99 (s, 1H), 6.50 (dd, J = 3.6, 1.8 Hz, 1H), 7.11 (dd, J = 3.6, 0.7 Hz, 1H), 7.58 (d, J = 1.8, 0.7 Hz, 1H); MS (ESI) m/z 355 (M+H)⁺.

Example C1(3R,4R,5R)-(-)-3,4-Dimethyl-5-hydroxymethyl-2-furanone

(R)-(+)-5-Hydroxymethyl-2(5H)-furanone (1.94 g, 17.0 mmol) was dissolved in anhydrous pyridine (60 ml), triphenylmethyl chloride (14.3 g, 51.2 mmol) was added to the solution at room temperature, and the mixture was stirred for 6 hr. Ethanol was added to the reaction solution at 0°C, and the mixture was stirred for one hr. The reaction solution was concentrated under reduced pressure, and the concentrate was subjected to azeotropic distillation twice with toluene and purified by column chromatographic separation on silica gel (hexane : ethyl acetate = 3 : 1 to 2 : 1) to give (R)-(+)-5-triphenylmethyloxymethyl-2(5H)-furanone (5.47 g, 90%).

¹H NMR (CDCl₃) δ 3.39 (dd, J = 10.0, 5.0 Hz, 1H), 3.41 (dd, J = 10.0, 5.0 Hz, 1H), 5.08 (dddd, J = 5.0, 5.0, 1.5, 1.5 Hz, 1H), 6.19 (dd, J = 6.0, 2.0 Hz, 1H), 7.2-7.5 (m, 16H); [α]_D +87° (c 0.7, CHCl₃).

Copper iodide (I) (6.49 g, 34.1 mmol) was suspended in anhydrous ether (120 ml) under an argon atmosphere, and a 1.0 M solution of methyllithium in ether (64.9 ml, 64.9 mmol) was added to the suspension at 0°C. The resultant colorless and transparent solution was cooled to -78°C, and chlorotrimethylsilane (4.3 ml, 34.0 mmol) was added thereto. The mixture was stirred for 15 min, and a solution of the compound prepared just above (6.06 g, 17.0 mmol) in anhydrous THF (8 ml) was added to the reaction solution, followed by stirring for 2 hr. The reaction solution was poured into a mixed solution of ethyl acetate and water, sodium thiosulfate was added thereto, and the mixture was stirred until the mixed solution became colorless and transparent, followed by separation. The organic layer was concentrated under reduced pressure. The concentrate was then purified by column chromatographic separation on silica gel (hexane : ethyl acetate = 3 : 1) to give (4R,5R)-(-)-4-methyl-5-triphenylmethyloxymethyl-2-furanone (4.50 g, 71%).

¹H NMR (CDCl₃) δ 1.16 (d, J = 7.0 Hz, 3H), 2.17 (dd, J = 17.5, 7.0 Hz, 1H), 2.48 (dddq, J = 8.0, 8.0, 8.0, 7.0 Hz, 1H), 2.82 (dd, J = 17.5, 8.0 Hz, 1H), 3.18 (dd, J = 11.0, 4.0 Hz, 1H), 3.42 (dd, J = 11.0, 3.0 Hz, 1H), 4.14 (ddd, J = 8.0, 4.0, 3.0 Hz, 1H), 7.2-7.5 (m, 15H); [α]_D -34° (c 1.2, CHCl₃).

The compound prepared just above (2.14 g, 5.77 mmol) was dissolved in anhydrous THF (43 ml) under an argon atmosphere, and a 1.0 M solution of lithiumbistrimethylsilylamide in hexane (5.48 ml, 5.48 mmol) was added to the solution at -78°C. The solution was stirred for one hr, methyl iodide (3.59 ml, 57.7 mmol) was added thereto, and the mixture was stirred for additional 2 hr. The reaction solution was poured into a mixed solution of ethyl acetate and water, followed by separation. The organic layer was concentrated under reduced pressure. The concentrate was then purified by column chromatographic separation on silica gel (hexane : ether = 5 : 2) to give (3R,4R,5R)-(-)-3,4-dimethyl-5-triphenylmethyloxymethyl-2-furanone (1.32 g, 60%).

¹H NMR (CDCl₃) δ 0.95 (d, J = 7.5 Hz, 3H), 1.16 (d, J = 7.5 Hz, 3H), 2.47 (ddq, J = 7.5, 7.5, 5.0 Hz, 1H), 2.87 (dq, J = 7.5, 7.5 Hz, 1H), 3.20 (dd, J = 10.5, 5.0 Hz, 1H), 3.40 (dd, J = 10.5, 5.0 Hz, 1H), 4.14 (q-like, J = 5.0 Hz, 1H), 7.2-7.5 (m, 15H); [α]_D -34° (c 1.2, CHCl₃).

The compound (2.09 g, 5.41 mmol) prepared just above was dissolved in a 90% aqueous methanol solution (60 ml), Amberlyst IR-15 (H⁺) (0.42 g) was added thereto, and a reaction was allowed to proceed at 80°C for 19 hr. The resin was removed from the reaction solution by filtration, and the mother liquor was concentrated under reduced pressure. The concentrate was then purified by column chromatographic separation on silica gel (methylene chloride : ethyl acetate = 3 : 1) to give the title compound (0.71 g, 92%).

¹H NMR (CDCl₃) δ 1.06 (d, J = 7.0 Hz, 3H), 1.18 (d, J = 7.5 Hz, 3H), 1.98 (t-like, J = 7.0 Hz, 1H), 2.55 (ddq, J = 7.5, 7.5, 7.0 Hz, 1H), 2.81 (dq, J = 7.5, 7.5 Hz, 1H), 3.70 (ddd, J = 12.5, 7.0, 5.0 Hz, 1H), 3.90 (ddd, J = 12.5, 7.0, 3.0 Hz, 1H), 4.14 (ddd, J = 7.5, 5.0, 3.0 Hz, 1H); [α]_D -56° (c 2.1, CHCl₃).

Example C2(3R,4R,5R)-(-)-5-Dimethoxymethyl-3,4-dimethyl-2-furanone

Oxalyl chloride (1.04 ml, 12.1 mmol) was dissolved in anhydrous methylene chloride (17.5 ml) under an argon atmosphere. The solution was cooled to -78°C, and a solution of DMSO (1.29 ml, 18.2 mmol) in anhydrous methylene chloride (2 ml) was dropwise added to the cooled solution. After foaming quieted down, a solution of the compound prepared in Example C1 (0.87 g, 6.07 mmol) in anhydrous methylene chloride (2 ml) was added to the reaction solution, and the mixture was stirred for 20 min. Triethylamine (4.23 ml, 30.3 mmol) was added thereto, and the mixture was stirred at -78°C for 15 min and then at room temperature for 15 min. The reaction solution was poured into a mixed solution (50 ml) composed of methyl orthoformate and methanol (= 4 : 1) and containing camphorsulfonic acid (7.75 g, 33.6 mmol), and a reaction was allowed to react at room temperature for 30 min. The reaction solution was concentrated under reduced pressure, and the concentrate was dissolved in a mixed solution of ethyl acetate and water, followed by separation. The organic phase was concentrated under reduced pressure, and the concentrate was then purified by column chromatographic separation on silica gel (hexane : ethyl acetate = 4 : 1) to give the title compound (1.10 g,

96%).

¹H NMR (CDCl₃) δ 1.02 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.5 Hz, 3H), 2.65 (ddq, J = 9.0, 7.5, 3.5 Hz, 1H), 2.85 (dq, J = 9.0, 7.5 Hz, 1H), 3.44 (s, 3H), 3.45 (s, 3H), 4.01 (dd, J = 3.5, 3.0 Hz, 1H), 4.36 (d, J = 3.0 Hz, 1H); MS (FAB) m/z 189 (M+H)⁺; [α]_D -4.0° (c 1.1, CHCl₃).

Example C3

(3R,4R,5R)-2-Benzenesulfonylmethyl-5-dimethoxymethyl-3,4-dimethyl-2-hydroxyoxolane

Methylphenylsulfone (0.98 g, 6.25 mmol) was dissolved in anhydrous THF (30 ml) under an argon atmosphere. The solution was cooled to -78°C, and a 1.6 M solution of n-butyllithium in hexane (3.6 ml, 5.76 mmol) was dropwise added to the cooled solution. The mixture was stirred for 30 min, a solution of the compound prepared in Example C2 (0.90 g, 4.80 mmol) in anhydrous THF (4 ml) was added thereto, and the mixture was stirred at -78°C for 30 min. After the completion of the reaction, an aqueous ammonium chloride solution was added, and the temperature of the mixture was raised to room temperature. The reaction solution was concentrated under reduced pressure, and ether was added to the concentrate, followed by separation. The organic layer was concentrated under reduced pressure, and the concentrate was then purified by column chromatographic separation on silica gel (methylene chloride : ethyl acetate = 15 : 1) to give the title compound (1.41 g, 85%).

¹H NMR (CDCl₃) : (major) δ 0.96 (d, J = 7.5 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.9-2.2 (m, 2H), 3.09 (s, 3H), 3.22 (s, 3H), 3.4-3.8 (m, 3H), 4.86 (s, 1H), 7.4-7.7 (m, 3H), 7.9-8.1 (m, 2H).

¹H NMR (CDCl₃) : (minor) δ 0.82 (d, J = 7.5 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 2.3-2.7 (m, 2H), 3.37 (s, 3H), 3.41 (s, 3H), 3.4-3.8 (m, 2H), 4.29 (d, J = 6.0 Hz, 1H), 4.75 (s, 1H), 7.4-7.7 (m, 3H), 7.9-8.1 (m, 2H).

Example C4

(3R,4R,5R)-1-Benzenesulfonyl-2,5-di(t-butyldimethylsilyloxy)-6,6-dimethoxy-3,4-dimethyl-1-hexene

The compound (0.54 g, 1.18 mmol) prepared in Example C3 was dissolved in anhydrous THF (20 ml) under an argon atmosphere, 2,6-lutidine (0.40 ml, 3.55 mmol) and t-butyldimethylsilyl trifluoromethanesulfonate (0.57 ml, 2.35 mmol) were successively added to the solution, and a reaction was allowed to react at room temperature for 13 hr. After the completion of the reaction, the reaction solution was concentrated under reduced pressure, and the concentrate was then purified by column chromatographic separation on silica gel (toluene : ether = 10 : 1) to give the title compound (0.61 g, 90%).

¹H NMR (CDCl₃) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.23 (s, 6H), 0.8-0.9 (m, 3H), 0.89 (s, 18H), 1.15 (d, J = 7.0 Hz, 3H), 1.5-1.6 (m, 1H), 2.37 (dq, J = 11.5, 7.5 Hz, 1H), 3.33 (s, 3H), 3.44 (s, 3H), 3.73 (dd, J = 7.0, 2.5 Hz, 1H), 4.12 (d, J = 7.0 Hz, 1H), 5.60 (s, 1H), 7.4-7.6 (m, 3H), 7.8-7.9 (m, 2H).

Example C5

(4R,4R,6R)-(+)-2-Benzenesulfonyl-4-(t-butyldimethylsilyloxy)-5,6-dimethyl-2-cyclohexen-1-one

The compound prepared in Example C4 (1.39 g, 2.43 mmol) was dissolved in anhydrous methylene chloride (30 ml) under an argon atmosphere. The solution was cooled to -78°C, and tin(IV) chloride (0.3 ml, 2.56 mmol) was dropwise added to the cooled solution. The reaction solution was stirred for one hr, tin(IV) chloride (0.6 ml, 5.12 mmol) was again dropwise added to the reaction solution, and the mixture was stirred for additional 2 hr. After the completion of the reaction, an aqueous sodium hydrogencarbonate solution was added thereto, and the temperature of the mixture was raised to room temperature, followed by separation. The organic layer was concentrated under reduced pressure, and the concentrate was then purified by column chromatographic separation on silica gel (toluene : ether = 15 : 1) to give the title compound (0.87 g, 91%).

¹H NMR (CDCl₃) δ 0.15 (s, 3H), 0.19 (s, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.95 (s, 9H), 1.05 (d, J = 7.0 Hz, 3H), 2.32 (dddq, J = 7.0, 5.0, 3.5, 1.5 Hz, 1H), 2.59 (dq, J = 7.0, 3.5 Hz, 1H), 4.89 (dd, J = 5.0, 1.5 Hz, 1H), 7.4-7.6 (m, 3H), 7.78 (t-like, J = 1.5 Hz, 1H), 7.8-7.9 (m, 2H); MS (FAB) m/z 395 (M+H)⁺; [α]_D +162° (c 1.2, CHCl₃).

Example C6

(2R,3R,4R)-(+)-4-t-Butyldimethylsilyloxy-2,3-dimethylcyclohexanone

The compound (0.41 g, 1.04 mmol) prepared in Example C5 was dissolved in a 90% aqueous 1,4-dioxane solution

EP 0 885 893 A1

(25 ml), and disodium hydrogenphosphate (0.59 g, 4.18 mmol) was added to the solution. Aluminum-mercury amalgam (aluminum: 0.42 g, 15 mmol) was added to the reaction solution, and the mixture was vigorously stirred at room temperature for 4 hr. After the completion of the reaction, the alumina was removed by filtration, and the filtrate was concentrated under reduced pressure. The concentrate was again dissolved in a mixed solution of ether and water, followed by separation. The organic layer was concentrated under reduced pressure, and the concentrate was then purified by column chromatographic separation on silica gel (hexane : ether = 6 : 1) to give the title compound (0.15 g, 56%).

¹H NMR(benzene-d₆) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.99 (s, 9H), 1.03 (d, J = 7.0 Hz, 3H), 1.5-1.6 (m, 1H), 1.75 (dddd, J = 12.5, 12.5, 10.5, 5.0 Hz, 1H), 1.86 (ddd, J = 13.5, 12.5, 7.0 Hz, 1H), 1.9-2.2 (m, 2H), 2.21 (ddd, J = 13.5, 5.0, 3.5 Hz, 1H), 3.88 (ddd, J = 10.0, 4.5, 4.5 Hz, 1H); [α]_D +24° (c 1.2, CHCl₃).

Example C7

(6R,7R,8S)-8-t-Butyldimethylsilyloxy-6,7-dimethylbicyclo[4.4.0]deca-1-en-3-one

The compound (0.18 g, 0.70 mmol) prepared in Example C6 was dissolved in anhydrous methylene chloride (3.6 ml) under an argon atmosphere. Hexamethyldisilazane (0.19 ml, 0.91 mmol) and trimethylsilane iodide (0.11 ml, 0.77 mmol) were successively added to the solution, and a reaction was allowed to react at room temperature for 30 min. The reaction solution was diluted with hexane, the resultant precipitate was removed through Florisil, and the filtrate was evaporated to dryness. The residue was dissolved in anhydrous THF (4.0 ml) under an argon atmosphere, and the solution was cooled to -78°C. A 1.0 M solution of methyllithium in ether (0.78 ml, 0.78 mmol) was added to the cooled solution, the temperature of the mixture was raised to room temperature, and the mixture was stirred for 30 min. The reaction solution was again cooled to -78°C, α-trimethylsilylmethyl vinyl ketone (0.24 g, 1.41 mmol) was added to the cooled solution, the temperature of the mixture was raised to 0°C, and the mixture was stirred for one hr. The reaction solution was diluted with ether, an aqueous ammonium chloride was added thereto, the temperature was raised to room temperature, followed by separation. The organic layer was evaporated to dryness. The residue was dissolved in methanol (3 ml), a 28% solution of sodium methoxide in methanol (0.14 g, 0.70 mmol) was added thereto, and a reaction was allowed to proceed at 50°C for 2 hr. Ammonium chloride was added to the reaction solution to pH 7, and the reaction solution was then concentrated under reduced pressure. The concentrate was then purified by column chromatographic separation on silica gel (hexane : ethyl acetate = 5 : 1) to give the title compound (0.12 g, 57%).

¹H NMR (CDCl₃) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.93 (s, 9H), 1.01 (d, J = 7.0 Hz, 3H), 1.30 (s, 3H), 1.42 (dq, J = 7.0, 3.0 Hz, 1H), 1.6-1.7 (m, 1H), 1.65 (ddd, J = 14.5, 14.5, 5.0 Hz, 1H), 1.90 (dddd, J = 14.0, 6.0, 5.0, 3.0 Hz, 1H), 2.00 (ddd, J = 14.5, 5.5, 3.0 Hz, 1H), 2.08 (ddd, J = 14.0, 3.0, 3.0 Hz, 1H), 2.31 (dddd, J = 18.0, 5.0, 3.0, 1.0 Hz, 1H), 2.47 (ddd, J = 18.0, 14.5, 5.5 Hz, 1H), 2.82 (dddd, J = 14.0, 14.0, 5.0, 2.0 Hz, 1H), 3.86 (br q, J = 3.0 Hz, 1H), 5.76 (br s, 1H); MS (FAB) m/z 309 (M+H)⁺; [α]_D +142° (c 1.0, CHCl₃).

Example C8

(4R,6R,7R,8S)-8-t-Butyldimethylsilyloxy-4-(1'-hydroxy-1'-methoxycarbonyl)ethyl-6,7-dimethylbicyclo[4.4.0]deca-1-en-3-one

The compound prepared in Example C7 (0.12 g, 0.40 mmol) was dissolved in anhydrous THF (3 ml) under an argon atmosphere, and a 1.0 M solution of lithiumbistrimethylsilylamide in hexane (2.0 ml, 2.0 mmol) was added to the solution at -78°C. The mixture was stirred for 30 min, a 1.0 M solution of zinc(II) chloride in ether (0.44 ml, 0.44 mmol) was poured into the mixture. The mixture was stirred for 10 min, methyl pyruvate (0.18 ml, 1.99 mmol) was dropwise added to the mixture, and the mixture was stirred for additional 30 min. Thereafter, the reaction solution was diluted with ether, an aqueous ammonium chloride solution was added thereto, the temperature was raised to room temperature, followed by separation. The organic layer was concentrated under reduced pressure, and the concentrate was then purified by column chromatographic separation on silica gel (hexane : ethyl acetate = 3 : 1) to give the title compound (0.16 g, 97%).

¹H NMR (CDCl₃) : (major) δ 0.07 (s, 6H), 0.93 (s, 9H), 1.02 (d, J = 7.0 Hz, 3H), 1.3-2.2 (m, 12H), 2.71 (dd, J = 13.5, 5.5 Hz, 1H), 2.80 (m, 1H), 3.73 (s, 3H), 3.86 (m, 1H), 4.87 (s, 1H), 5.75 (d, J = 2.0 Hz, 1H);

¹H NMR (CDCl₃) : (minor) δ 0.07 (s, 6H), 0.93 (s, 9H), 1.05 (d, J = 7.0 Hz, 3H), 1.3-2.2 (m, 12H), 2.80 (m, 1H), 3.03 (dd, J = 15.0, 5.0 Hz, 1H), 3.36 (s, 1H), 3.81 (s, 3H), 3.86 (m, 1H), 5.72 (d, J = 2.0 Hz, 1H).

Example C9(4aR,5R,6S)-(-)-6-Hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-b]furan-2(4H)-one

5 The compound prepared in Example C8 (0.16 g, 0.39 mmol) was dissolved in a 90% aqueous 1,4-dioxane solution (8 ml), camphorsulfonic acid (0.10 g, 0.44 mmol) was added thereto, and a reaction was allowed to proceed at 105°C for 28 hr. The reaction solution was neutralized with sodium hydrogencarbonate to pH 7 and then concentrated under reduced pressure. The concentrate was then purified by column chromatographic separation on silica gel (toluene : ether = 2 : 1) to give the title compound (49 mg, 51%).

10 ¹H NMR (CDCl₃) δ 1.18 (s, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.76 (dq, J = 7.0, 2.0 Hz, 1H), 1.91 (br s, 3H), 2.20 (br d, J = 16.0 Hz, 1H), 2.42 (dd, J = 20.0, 4.0 Hz, 1H), 2.59 (ddd, J = 20.0, 4.0, 3.0 Hz, 1H), 2.83 (d, J = 16.0 Hz, 1H), 4.04 (br s, 1H), 5.76 (br t, J = 4.0 Hz, 1H), 5.99 (s, 1H); MS (FAB) m/z 247 (M+H)⁺; [α]_D -224° (c 0.5, CHCl₃).

Example C10

15

Substance PF1092C

Selenium dioxide (36 mg, 0.32 mmol) was suspended in a 97% aqueous 1,4-dioxane solution (0.6 ml), and the suspension was stirred at 105°C for 30 min. The compound prepared in Example C9 (27 mg, 0.11 mmol) was added to the reaction solution, and a reaction was allowed to proceed at 105°C for 21 hr. Thereafter, the reaction solution was diluted with ether, an aqueous sodium thiosulfate was added thereto, and the stirring was continued until the organic phase became transparent, followed by separation. The organic layer was concentrated under reduced pressure, and the concentrate was then purified by column chromatographic separation on silica gel (toluene : ethyl acetate = 1 : 1) to give the title compound (a compound represented by the general formula (I) wherein R¹ and R² represent a hydrogen atom) (15 mg, 53%).

25 m.p.: 169-174°C (decomp.), white acicular crystal (recrystallized from toluene)

¹H NMR (CDCl₃) δ 1.21 (s, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.80 (dq, J = 7.0, 1.5 Hz, 1H), 1.92 (br s, 3H), 2.19 (br d, J = 16.0 Hz, 1H), 2.27 (d, J = 3.0 Hz, 1H), 2.29 (d, J = 8.0 Hz, 1H), 2.85 (d, J = 16.0 Hz, 1H), 3.94 (ddd, J = 5.0, 3.0, 1.5 Hz, 1H), 4.39 (ddd, J = 8.0, 5.0, 2.0 Hz, 1H), 5.66 (br s, 1H), 5.99 (s, 1H); MS (EI) m/z 262 (M)⁺; [α]_D -97° (c 0.5, CHCl₃).

30

Example C11Substance PF1092A

35

The compound prepared in Example C10 (19 mg, 0.07 mmol) was dissolved in anhydrous DMF (0.4 ml), imidazole (50 mg, 0.73 mmol) and t-butyldimethylsilyl chloride (65 mg, 0.43 mmol) were added to the solution, and the mixture was stirred at room temperature for 7 hr. Thereafter, the reaction solution was diluted with chloroform and washed with a 5% aqueous potassium hydrogensulfate solution and an aqueous sodium hydrogencarbonate solution in that order. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The concentrate was purified by preparative TLC separation (toluene : ethyl acetate = 10 : 1) to give a corresponding t-butyldimethylsilyl form (23 mg, 85%).

40 The compound prepared just above (21 mg, 0.06 mmol) was dissolved in methylene chloride (0.45 ml), pyridine (22 μl, 0.27 mmol) and acetyl chloride (17 μl, 0.24 mmol) were added to the solution under ice cooling, the mixture was stirred under ice cooling for 30 min, the temperature was raised to room temperature, and the mixture was stirred at room temperature for additional 22 hr. The reaction solution was diluted with chloroform and washed with a 5% aqueous potassium hydrogensulfate solution and an aqueous sodium hydrogencarbonate solution in that order. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The concentrate was purified by preparative TLC separation (toluene : ethyl acetate = 20 : 1) to give a corresponding acetyl form (21 mg, 89%).

50

The compound prepared just above (18 mg, 0.04 mmol) was dissolved in anhydrous THF (0.5 ml), hydrogen fluoride-pyridine complex (33 μl, 0.40 mmol) was added to the solution under ice cooling, the mixture was stirred under ice cooling for 30 min, the temperature was raised to room temperature, and the mixture was stirred for additional 2 hr. The reaction solution was diluted with chloroform and washed with a 5% aqueous potassium hydrogensulfate solution and an aqueous sodium hydrogencarbonate solution in that order. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The concentrate was purified by preparative TLC separation (hexane : ethyl acetate = 1 : 1) to give the title compound (a compound represented by the general formula (I) wherein R¹ represents an acetyl group and R² represents a hydrogen atom) (5.5 mg, 42%).

55

EP 0 885 893 A1

Various spectral data of the title compound were in agreement with those of substance PF1092A disclosed in Japanese Patent Laid-Open No. 253467/1996.

Example C12

Substance PF1092B

The compound prepared in Example C10 (15 mg, 0.06 mmol) was dissolved in anhydrous methylene chloride (0.3 ml), diisopropylethylamine (25 μ l, 0.14 mmol) and acetyl chloride (9 μ l, 0.13 mmol) were added to the solution under ice cooling, the mixture was stirred under ice cooling for 30 min, the temperature was raised to room temperature, and the mixture was stirred for 17 hr. The reaction solution was diluted with chloroform and washed with a 5% aqueous potassium hydrogensulfate solution and an aqueous sodium hydrogencarbonate solution in that order. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The concentrate was purified by preparative TLC separation (hexane : ethyl acetate = 1 : 1) to give the title compound (a compound represented by the general formula (I) wherein R¹ represents a hydrogen atom and R² represents an acetyl group) (7.8 mg, 45%).

Various spectral data of the title compound were in agreement with those of substance PF1092B disclosed in Japanese Patent Laid-Open No. 253467/1996.

Activity Evaluation Test

The progesterone receptor binding activity of the compounds of the present invention was measured in the following manner in accordance with the method of H. Kondo et. al. (J. Antibiotics, Vol. 43, pp. 1533-1542, 1990).

That is, uteri taken from hogs in 5 mM phosphate buffer were disrupted using Polytron homogenizer, and the resulting solution was centrifuged (100,000 x g, 30 min) to separate the supernatant, thereby preparing a cytosol containing progesterone receptor. A given concentration of a test drug solution (10 μ l) was added to a solution composed of 50 μ l of the cytosol obtained just above (2-3 mg protein/ml) and 40 μ l of a solution of [³H]-progesterone as a ligand (3.84 TBq/mmol, 18.5 kBq/ml), and they were incubated in a test tube for 60 min at 4°C to effect a reaction. Then, 100 μ l of a 0.5% activated carbon solution was added to the reaction solution, and the mixture was allowed to stand for 10 min and then centrifuged (2,000 x g, 10 min). The radioactivity of the supernatant was measured with a liquid scintillation counter.

Separately, the radioactivity was measured in the same manner as described above, except that no test drug was added. Further, the radioactivity was measured in the same manner as described above, except that 10 μ l of Medroxyprogesterone Acetate (MPA) (10 μ g/ml) was added instead of the test drug. The radioactivity with no test drug added was defined as the amount of total binding of [³H]-progesterone to the cytosol, and the radioactivity with MPA added was defined as the amount of non-specific binding. The inhibition ratio was calculated from these measured values by the following equation to determine the binding inhibitory activity (IC₅₀).

$$\text{Inhibition ratio (\%)} = \left(1 - \frac{(\text{total binding amount with test drug added}) - (\text{non-specific binding amount})}{(\text{total binding amount with no test drug added}) - (\text{non-specific binding amount})} \right) \times 100$$

The compounds prepared in Examples A1, A3, A4, A6b, A7, A8, A10, A12, A17, A19, A21, A23, A30, A41, A44, and A45, the compounds prepared in Examples B2, B4, B7, B8, B27, B28, B30, and B42, and Mifepristone (RU38486) had the following inhibitory activity against progesterone receptor binding.

Table 1

Inhibitory activity against progesterone receptor binding	
Ex. No. of compound	Inhibitory activity (IC ₅₀) (nM)
A3	12
A17	17
A23	18
A21	27
A45	29

EP 0 885 893 A1

Table 1 (continued)

Inhibitory activity against progesterone receptor binding	
Ex. No. of compound	Inhibitory activity (IC ₅₀) (nM)
A4	32
A19	47
A30	47
A10	75
A12	83
A8	97
A44	276
A6b	288
A41	400
A1	1000
A7	2840
B2	55
B4	53
B7	54
B8 (Racemic modification)	74
B8 (Natural type)	21
B27	39
B28	66
B30	60
B42 (Nonnatural type)	797
B42 (Natural type)	33
RU38486	106

EXAMPLE D1

A medium composed of 2.0% of starch, 1.0% of glucose, 0.5% of polypeptone, 0.6% of wheat germ, 0.3% of yeast extract, 0.2% of soybean meal and 0.2% of calcium carbonate (pH 7.0 before sterilization) was used as a seed culture medium. Another medium prepared by adding 0.3% of soybean meal to sufficiently water-absorbed rice was used as a production medium.

A 20 ml portion of the seed culture medium dispensed in a 100 ml capacity conical flask was sterilized at 120 °C for 15 minutes, and one loopful of *Penicillium* sp. PF1092 (FERM BP-5350) cells grown on a slant agar medium were inoculated into the medium and cultured at 25°C for 3 days on a shaker to obtain a seed culture. Next, a 100 g portion of the aforementioned production medium dispensed in a 500 ml capacity conical flask was sterilized at 120°C for 15 minutes, and 5 ml of the just obtained seed culture was inoculated into the medium, mixed thoroughly and then subjected to 10 days of static culturing at 28°C.

EXAMPLE D2

A 6 kg portion of the thus obtained culture mixture was extracted with 12 liters of ethyl acetate, and the resulting ethyl acetate layer containing active components was evaporated to obtain 15.3 g of oily material. The thus obtained oily material was applied to a column packed with 400 g of silica gel (Wakogel C-200, manufactured by Wako Pure Chemical Industries), washed with chloroform and then chromatographed using chloroform-methanol (100:1 to 1 OO:3) as a developing solvent, and the resulting active fraction was evaporated to obtain 4.6 g of crude powder. Next, the

EP 0 885 893 A1

crude powder was applied to a column packed with 150 g of silica gel (Wakogel C-200, manufactured by Wako Pure Chemical Industries), washed with hexane-ethyl acetate (8:1 to 5:1) and then chromatographed using hexane-ethyl to acetate (4:1 to 3:1) as a developing solvent to effect elution of substance PF1092B, and the resulting active fraction was evaporated to obtain 282 mg of crude powder containing substance PF1092B. The chromatography was continued using hexane-ethyl acetate (2:1 to 1:1) as a developing solvent to effect elution of substance PF1092A and substance PF1092C, and the resulting active fraction was evaporated to obtain 763 mg of crude powder containing substance PF1092A and substance PF1092C. Next, the crude powder containing substance PF1092B was purified by Sephadex LH-20 (700 ml, manufactured by Pharmacia) column chromatography using chloroform-methanol (1:1) as a developing solvent, and the active fraction containing substance PF1092B was evaporated to obtain 157.0 mg of substance PF1092B as colorless powder. The colorless powder of substance PF1092B was then dissolved in a chloroform-methanol mixture and allowed to stand to obtain 49.1 mg of substance PF1092B as colorless needle crystals.

On the other hand, the crude powder containing substance PF1092A and substance PF1092C obtained by the silica gel column chromatography using hexane-ethyl acetate (2:1 to 1:1) as a developing solvent was purified by Sephadex LH-20 (700 ml) column chromatography using chloroform-methanol (1:1) as a developing solvent to obtain 298 mg of substance PF1092A as colorless powder and then 159 mg of substance PF1092C as colorless powder. Thereafter, the colorless powder of substance PF1092A was dissolved in a chloroform-methanol mixture and allowed to stand to obtain 60.0 mg of substance PF1092A as colorless needle crystals, and the colorless powder of substance PF1092C was dissolved in ethyl acetate and allowed to stand to obtain 30.1 mg of substance PF1092C as colorless needle crystals. These substances have the aforementioned physico-chemical properties.

Structures of the compounds of the above examples are summarized in the following table.

Table 2








Example	R ¹	R ²	R ³	R ⁴	R ⁵
A 1	C ₂ H ₅ CO-O-	HO-	H	CH ₃	H
A 2	HO-	C ₂ H ₅ CO-O-	H	CH ₃	H
A 3	HO-	 -CO-O-	H	CH ₃	H
A 4	C ₂ H ₅ CO-O-	C ₂ H ₅ CO-O-	H	CH ₃	H
A 6a	C ₃ H ₇ NHCO-O-	HO-	H	CH ₃	H
A 6b	HO-	C ₃ H ₇ NHCO-O-	H	CH ₃	H
A 6c	C ₃ H ₇ NHCO-O-	C ₃ H ₇ NHCO-O-	H	CH ₃	H
A 7	 -CH ₂ -O-	HO-	H	CH ₃	H
A 8	CH ₃ OCH ₂ O-	 -CO-O-	H	CH ₃	H
A 9	HO-	 O-	H	CH ₃	H
A 10	CH ₃ O-	C ₂ H ₅ CO-O-	H	CH ₃	H
A 11a	HO-	CH ₃ CONH-	H	CH ₃	H
A 11b	HO-	CH ₃ CONH-	H	CH ₃	H
A 12	HO-	Cl-CH ₂ CO-O-	H	CH ₃	H
A 13	HO-	 -CH ₂ CO-O-	H	CH ₃	H
A 14	C ₂ H ₅ CO-O-	 -CO-O-	H	CH ₃	H
A 15	 -CO-O-	C ₂ H ₅ CO-O-	H	CH ₃	H

Table 2 (cont.)















Example	R ¹	R ²	R ³	R ⁴	R ⁵
A16	HO-	(CH ₃) ₂ CHCO-O-	H	CH ₃	H
A17	HO-	 CO-O-	H	CH ₃	H
A18	 CO-O-	HO-	H	CH ₃	H
A19	HO-	 CO-O-	H	CH ₃	H
A20	HO-	 CH=CH-CO-O-	H	CH ₃	H
A21	HO-	 CO-O-	H	CH ₃	H
A22	O ₂ N-  CO-O-	HO-	H	CH ₃	H
A23	HO-	O ₂ N-  CO-O-	H	CH ₃	H
A24	 CO-O-	 CO-O-	H	CH ₃	H
A25	HO-	 CO-O-	H	CH ₃	H
A26	HO-	 CO-O-	H	CH ₃	H
A27	CH ₃ NHCO-O-	HO-	H	CH ₃	H
A28	 NHCO-O-	 NHCO-O-	H	CH ₃	H
A29	CH ₃ -O-	CH ₃ -O-	H	CH ₃	H
A30	CH ₃ -O-	CH ₃ -CO-O-	H	CH ₃	H
A31	CH ₃ -O-	 CO-O-	H	CH ₃	H

Table 2 (cont.)










Example	R ¹	R ²	R ³	R ⁴	R ⁵
A32	CH ₃ -O-	 -CO-O-	H	CH ₃	H
A33	C ₃ H ₇ O-	CH ₃ CO-O-	H	CH ₃	H
A34	CH ₃ -O-	C ₂ H ₅ O-CO-O-	H	CH ₃	H
A35	CH ₃ -O-	 -O-CO-O-	H	CH ₃	H
A36	C ₂ H ₅ CO-O-	CH ₃ -O-CH ₂ -O-	H	CH ₃	H
A37	 -CO-O-	CH ₃ -O-CH ₂ -O-	H	CH ₃	H
A38	CH ₃ OC ₂ H ₄ OCH ₂ O-	 -CO-O-	H	CH ₃	H
A39	CH ₃ O-	 -CO-O-	H	CH ₃	H
A40	C ₂ H ₅ O-	 -CO-O-	H	CH ₃	H
A41	C ₂ H ₅ O-	 -CO-O-	H	CH ₃	H
A42	CH ₃ O-	CH ₃ O-	H	CH ₃	H
A43	CH ₃ O-	CH ₃ SO ₂ -O-	H	CH ₃	H
A44	CH ₃ CO-O-	 -CO-O-	H	CH ₃	H
A45	HO-	 -CO-O-	H	CH ₃	H
A46	CH ₃ O-	CH ₃ CONH-	H	CH ₃	H

Table 2 (cont.)














Example	R ¹	R ²	R ³	R ⁴	R ⁵
B 1	H	HO-	H	CH ₃	H
B 2	H	CH ₃ CO-O-	H	CH ₃	H
B 3	H	C ₂ H ₅ CO-O-	H	CH ₃	H
B 4	H	C ₃ H ₇ CO-O-	H	CH ₃	H
B 5	H	(CH ₃) ₂ CHCO-O-	H	CH ₃	H
B 6	H	(CH ₃) ₂ CHCH ₂ CO-O-	H	CH ₃	H
B 7	H	 -CO-O-	H	CH ₃	H
B 8	H	 -CO-O-	H	CH ₃	H
B 9	H	 -CO-O-	H	CH ₃	H
B 13	H	HO-	H	CH ₃	CH ₃
B 14	H	CH ₃ CO-O-	H	CH ₃	CH ₃
B 15	H	C ₂ H ₅ CO-O-	H	CH ₃	CH ₃
B 16	H	 -CO-O-	H	CH ₃	CH ₃
B 17	H	 -CO-O-	H	CH ₃	CH ₃
B 20	H	HO-	H	C ₂ H ₅	H
B 21	H	CH ₃ CO-O-	H	C ₂ H ₅	H
B 22	H	C ₂ H ₅ CO-O-	H	C ₂ H ₅	H
B 23	H	 -CO-O-	H	C ₂ H ₅	H
B 24	H	 -CO-O-	H	C ₂ H ₅	H

Table 2 (cont.)

Example	R ¹	R ²	R ³	R ⁴	R ⁵
B26	H	HO-	H	H	H
B27	H	CH ₃ CO-O-	H	H	H
B28	H	C ₂ H ₅ CO-O-	H	H	H
B29	H	 -CO-O-	H	H	H
B30	H	 -CO-O-	H	H	H
B34	H	HO-	CH ₃	H	H
B35	H	CH ₃ CO-O-	CH ₃	H	H
B36	H	C ₂ H ₅ CO-O-	CH ₃	H	H
B37	H	 -CO-O-	CH ₃	H	H
B38	H	 -CO-O-	CH ₃	H	H
B39	HO-	HO-	H	CH ₃	H
B40	HO-	HO-	H	CH ₃	CH ₃
B41	HO-	HO-	H	C ₂ H ₅	H
B46	CH ₃	HO-	H	CH ₃	H
B47	CH ₃	CH ₃ CO-O-	H	CH ₃	H
B48	CH ₃	C ₂ H ₅ CO-O-	H	CH ₃	H
B49	CH ₃	 -CO-O-	H	CH ₃	H
B50	CH ₃	 -CO-O-	H	CH ₃	H

Preparation Tablets

The compound of Example A4, lactose, crosslinked polyvidone, hydroxypropylmethyl cellulose were granulated by the wet process, and magnesium stearate was added thereto.

The mixture was then compressed to prepare tablets. Each tablet had the following composition.

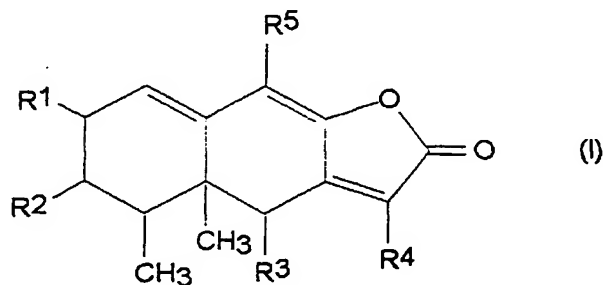
Compound of Examl A4	5.0 mg
Lactose	185 mg
Crosslinked polyvidone	7.0 mg
Hydroxypropylmethyl cellulose	2.5 mg
Magnesium stearate	0.5 mg
Total	200 mg

Acute Toxicity

The compound of Example A4 dissolved in 0.2 % of methylcellulose solution was hypodermically administered to SD male rat (16 weeks old) at a dose of 60 mg/kg. As a result, all the animals survived and there is no significant toxicity.

Claims

1. A compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



wherein

R¹ represents
a hydroxyl group,
optionally substituted C₁-C₁₀ alkyloxy,
optionally substituted C₂-C₁₀ alkenyloxy,
optionally substituted C₂-C₁₀ alkynyloxy,
C₃-C₆ cycloalkyloxy,
C₂-C₁₂ alkoxyalkyloxy,
five- or six-membered cycloalkyloxy containig one oxygen atom,
optionally substituted C₇-C₁₅ aralkyloxy,
optionally substituted C₂-C₁₁ alkylcarbonyloxy,
optionally substituted C₃-C₁₁ alkenylcarbonyloxy,
optionally substituted C₃-C₁₁ alkynylcarbonyloxy,
C₄-C₁₅ cycloalkylcarbonyloxy,
C₂-C₁₁ alkoxy carbonyloxy,
C₇-C₁₅ aryloxy carbonyloxy.

optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 optionally substituted C₇-C₁₅ aromatic acyloxy,
 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group
 consisting of nitrogen, oxygen, and sulfur atoms,
 5 optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from
 the group consisting of nitrogen, oxygen, and sulfur atoms,
 C₁-C₆ alkylsulfonyloxy,
 optionally substituted C₆-C₁₂ aromatic sulfonyloxy,
 C₂-C₇ alkylcarbamoyloxy
 10 optionally substituted C₇-C₁₂ aromatic carbamoyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonylamino,
 optionally substituted C₇-C₁₅ aromatic acylamino,
 a hydrogen atom,
 optionally substituted C₁-C₁₀ alkyl,
 15 optionally substituted C₂-C₁₀ alkenyl, or
 optionally substituted C₂-C₁₀ alkynyl;
 R² represents
 a hydroxyl group,
 optionally substituted C₁-C₁₀ alkyloxy,
 20 optionally substituted C₂-C₁₀ alkenyloxy,
 optionally substituted C₂-C₁₀ alkynyloxy,
 C₃-C₆ cycloalkyloxy,
 C₂-C₁₂ alkoxyalkyloxy,
 five- or six-membered cycloalkyloxy containig one oxygen atom,
 25 optionally substituted C₇-C₁₅ aralkyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonyloxy,
 optionally substituted C₃-C₁₁ alkenylcarbonyloxy,
 optionally substituted C₃-C₁₁ alkynylcarbonyloxy,
 C₄-C₁₅ cycloalkylcarbonyloxy,
 30 C₂-C₁₁ alkoxy carbonyloxy,
 C₇-C₁₅ aryloxy carbonyloxy,
 optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 optionally substituted C₇-C₁₅ aromatic acyloxy,
 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group
 35 consisting of nitrogen, oxygen, and sulfur atoms,
 optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from
 the group consisting of nitrogen, oxygen, and sulfur atoms,
 C₁-C₆ alkylsulfonyloxy,
 optionally substituted C₆-C₁₂ aromatic sulfonyloxy,
 40 C₂-C₇ alkylcarbamoyloxy
 optionally substituted C₇-C₁₂ aromatic carbamoyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonylamino,
 optionally substituted C₇-C₁₅ aromatic acylamino;
 R³ represents
 45 a hydrogen atom
 optionally substituted C₁-C₁₀ alkyl, or
 optionally substituted C₂-C₁₀ alkenyl;
 R⁴ represents
 a hydrogen atom
 50 optionally substituted C₁-C₁₀ alkyl, or
 optionally substituted C₂-C₁₀ alkenyl; and
 R⁵ represents
 a hydrogen atom
 55 optionally substituted C₁-C₁₀ alkyl, or
 optionally substituted C₂-C₁₀ alkenyl,

provided that a compound wherein both R¹ and R² represent a hydroxyl group, R³ and R⁵ represent a hydrogen
 atom, and R⁴ represents methyl, a compound wherein R¹ represents methylcarbonyloxy, and R² represents a

hydroxyl group, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl, a compound wherein R¹ represents a hydroxyl group, R² represent methylcarbonyloxy, R³ and R⁵ represent a hydrogen atom, and R⁴ represents methyl are excluded.

2. The compound according to claim 1, wherein

R¹ represents
 a hydroxyl group,
 C₁-C₁₀ alkyloxy,
 C₃-C₆ cycloalkyloxy,
 C₂-C₁₂ alkoxyalkyloxy,
 optionally substituted C₇-C₁₅ aralkyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonyloxy,
 C₄-C₁₅ cycloalkylcarbonyloxy,
 C₂-C₁₁ alkoxycarbonyloxy,
 C₇-C₁₅ aryloxy carbonyloxy,
 optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 optionally substituted C₇-C₁₅ aromatic acyloxy,
 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group
 consisting of nitrogen, oxygen, and sulfur atoms,
 optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from
 the group consisting of nitrogen, oxygen, and sulfur atoms,
 C₁-C₆ alkylsulfonyloxy,
 C₂-C₇ alkylcarbamoxyloxy
 optionally substituted C₇-C₁₂ aromatic carbamoxyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonylamino,
 a hydrogen atom, or
 optionally substituted C₁-C₁₀ alkyl;
 R² represents a hydroxyl group;
 R³ represents
 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl;
 R⁴ represents
 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl; and
 R⁵ represents
 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl.

3. The compound according to claim 1, wherein

R¹ represents a hydroxyl group;
 R² represents
 a hydroxyl group,
 C₁-C₁₀ alkyloxy,
 C₃-C₆ cycloalkyloxy,
 C₂-C₁₂ alkoxyalkyloxy,
 optionally substituted C₇-C₁₅ aralkyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonyloxy,
 C₄-C₁₅ cycloalkylcarbonyloxy,
 C₂-C₁₁ alkoxycarbonyloxy,
 C₇-C₁₅ aryloxy carbonyloxy,
 optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 optionally substituted C₇-C₁₅ aromatic acyloxy,
 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group
 consisting of nitrogen, oxygen, and sulfur atoms,
 optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from
 the group consisting of nitrogen, oxygen, and sulfur atoms,

C₁-C₆ alkylsulfonyloxy,
 C₂-C₇ alkylcarbamoyloxy
 optionally substituted C₇-C₁₂ aromatic carbamoyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonylamino,
 5 a hydrogen atom, or
 optionally substituted C₁-C₁₀ alkyl;
 R³ represents
 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl;
 10 R⁴ represents
 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl; and
 R⁵ represents
 a hydrogen atom or
 15 optionally substituted C₁-C₁₀ alkyl.

4. The compound according to claim 1, wherein

R¹ and R² each independently represent
 20 a hydroxyl group;
 C₁-C₁₀ alkyloxy,
 C₃-C₆ cycloalkyloxy,
 C₂-C₁₂ alkoxyalkyloxy,
 optionally substituted C₇-C₁₅ aralkyloxy,
 25 optionally substituted C₂-C₁₁ alkylcarbonyloxy,
 C₄-C₁₅ cycloalkylcarbonyloxy,
 C₂-C₁₁ alkoxycarbonyloxy,
 C₇-C₁₅ aryloxy carbonyloxy,
 optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 30 optionally substituted C₇-C₁₅ aromatic acyloxy,
 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group
 consisting of nitrogen, oxygen, and sulfur atoms,
 optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from
 the group consisting of nitrogen, oxygen, and sulfur atoms,
 35 C₁-C₆ alkylsulfonyloxy,
 C₂-C₇ alkylcarbamoyloxy
 optionally substituted C₇-C₁₂ aromatic carbamoyloxy,
 optionally substituted C₂-C₁₁ alkylcarbonylamino,
 a hydrogen atom, or
 40 optionally substituted C₁-C₁₀ alkyl;
 R³ represents
 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl;
 R⁴ represents
 45 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl; and
 R⁵ represents
 a hydrogen atom or
 optionally substituted C₁-C₁₀ alkyl.
 50

5. The compound according to claim 1, wherein

R¹ represents a hydrogen atom;
 R² represents
 55 a hydroxyl group,
 C₂-C₁₀ alkylcarbonyloxy,
 C₃-C₁₀ alkenylcarbonyloxy,
 optionally substituted C₂-C₁₀ alkylcarbonyloxy,

C₄-C₁₅ cycloalkylcarbonyloxy,
 optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
 optionally substituted C₇-C₁₅ aromatic acyloxy, or
 optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one nitrogen, oxygen, or sulfur atom;

R³ represents

a hydrogen atom

optionally substituted C₁-C₁₀ alkyl, or

optionally substituted C₂-C₁₀ alkenyl;

R⁴ represents

a hydrogen atom,

C₁-C₁₀ alkyl,

optionally substituted C₁-C₁₀ alkyl,

optionally substituted C₂-C₁₀ alkenyl; and

R⁵ represents

a hydrogen atom

optionally substituted C₁-C₁₀ alkyl, or

optionally substituted C₂-C₁₀ alkenyl.

6. The compound according to claim 1, wherein

R² represents 2-tetrahydropyranyloxy, propionyloxy, isobutyryloxy, chloroacetyloxy, phenylacetyloxy, cyclopropylcarbonyloxy, cyclohexylcarbonyloxy, cinnamoyloxy, benzoyloxy, 4-nitrobenzoyloxy, 2-thenoyloxy, 2-furoyloxy, 1-benzothiophen-2-ylcarbonyloxy, 4-methyl-5-thiazolylcarbonyloxy, n-propylcarbamoyloxy, or acetylamino, and
 R¹ represents a hydroxyl group.

7. The compound according to claim 1, wherein

R² represents methoxy, acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, 2-furoyloxy, ethoxycarbonyloxy, phenoxycarbonyloxy, methylsulfonyloxy, or acetylamino; and
 R¹ represents methoxy.

8. The compound according to claim 1, wherein

R² represents acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy; and
 R¹ represents ethoxy.

9. The compound according to claim 1, wherein

R² represents acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy; and
 R¹ represents n-propyloxy.

10. The compound according to claim 1, wherein

R² represents a hydroxyl group, acetyloxy, propionyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-furoyloxy, 2-thenoyloxy, or methoxymethyloxy; and
 R¹ represents propionyloxy.

11. The compound according to claim 1, wherein

R² represents a hydroxyl group,
 R¹ represents benzyloxy, cyclopropylcarbonyloxy, cyclohexylcarbonyloxy, benzoyloxy, 4-nitrobenzoyloxy, 2-thenoyloxy, 2-furoyloxy, methylcarbamoyloxy, or n-propylcarbamoyloxy.

12. The compound according to claim 1, wherein

R² represents 2-furoyloxy; and
 R¹ represents acetyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy.

13. The compound according to claim 1, wherein

R² represents propionyloxy; and
R¹ represents acetyloxy, cyclopropylcarbonyloxy, benzoyloxy, 2-thenoyloxy, or 2-furoyloxy.

14. The compound according to claim 1, wherein

R² represents benzoyloxy; and
R¹ represents methoxymethyloxy or methoxyethoxymethyloxy.

15. The compound according to claim 1, wherein

R² represents methoxymethyloxy; and
R¹ represents benzoyloxy.

16. The compound according to claim 1, wherein

R² represents n-propylcarbamoyloxy; and
R¹ represents n-propylcarbamoyloxy.

17. The compound according to claim 1, wherein

R² represents phenylcarbamoyloxy; and
R¹ represents phenylcarbamoyloxy.

18. The compound according to claim 1, wherein

R¹ represents a hydrogen atom;
R² represents a hydroxyl atom, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy;
R³ represents a hydrogen atom;
R⁴ represents methyl; and
R⁵ represents a hydrogen atom.

19. The compound according to claim 1, wherein

R¹ represents a hydrogen atom;
R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy;
R³ represents a hydrogen atom;
R⁴ represents methyl; and
R⁵ represents methyl.

20. The compound according to claim 1, wherein

R¹ represents a hydrogen atom;
R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy;
R³ represents a hydrogen atom;
R⁴ represents ethyl; and
R⁵ represents a hydrogen atom.

21. The compound according to claim 1, wherein

R¹ represents a hydrogen atom;
R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy;
R³ represents a hydrogen atom;

R⁴ represents a hydrogen atom; and
R⁵ represents a hydrogen atom.

22. The compound according to claim 1, wherein

R¹ represents a hydrogen atom;
R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy;
R³ represents methyl;
R⁴ represents methyl; and
R⁵ represents a hydrogen atom.

23. The compound according to claim 1, wherein

R¹ represents methyl;
R² represents a hydroxyl group, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, isovaleryloxy, benzoyloxy, 2-furoyloxy, or 2-thenoyloxy;
R³ represents a hydrogen atom;
R⁴ represents methyl; and
R⁵ represents a hydrogen atom.

24. The compound according to claim 1, wherein

R¹ and R² each independently represent
a hydroxyl group,
optionally substituted C₁-C₁₀ alkyloxy,
optionally substituted C₂-C₁₀ alkenyloxy,
optionally substituted C₂-C₁₀ alkynyloxy,
C₃-C₆ cycloalkyloxy,
C₂-C₁₂ alkoxyalkyloxy,
five- or six-membered cycloalkyloxy containig one oxygen atom,
optionally substituted C₇-C₁₅ aralkyloxy,
optionally substituted C₂-C₁₁ alkylcarbonyloxy,
optionally substituted C₃-C₁₁ alkenylcarbonyloxy,
optionally substituted C₃-C₁₁ alkynylcarbonyloxy,
C₄-C₁₅ cycloalkylcarbonyloxy,
C₂-C₁₁ alkoxy carbonyloxy,
C₇-C₁₅ aryloxy carbonyloxy,
optionally substituted C₈-C₁₅ aralkylcarbonyloxy,
optionally substituted C₇-C₁₅ aromatic acyloxy,
optionally substituted C₃-C₁₅ heteroaromatic acyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,
optionally substituted C₄-C₁₂ saturated heterocyclic carbonyloxy having at least one hetero atom selected from the group consisting of nitrogen, oxygen, and sulfur atoms,
C₁-C₆ alkylsulfonyloxy,
optionally substituted C₆-C₁₂ aromatic sulfonyloxy,
C₂-C₇ alkylcarbamoyloxy
optionally substituted C₇-C₁₂ aromatic carbamoyloxy,
optionally substituted C₂-C₁₁ alkylcarbonylamino;
R³ represents a hydrogen atom;
R⁴ represents
a hydrogen atom or
C₁-C₁₀ alkyl; and
R⁵ represents a hydrogen atom.

25. The compound according to claim 2, wherein

R¹ and R² each independently represent

a hydroxyl group,
 C₁-C₆ alkoxy group,
 C₂-C₁₂ alkoxyalkoxy which may be substituted by C₁-C₆ alkoxy group,
 C₇-C₁₅ aralkyloxy,
 C₂-C₇ alkylcarbonyloxy which may be substituted by a halogen,
 C₄-C₁₅ cycloalkylcarbonyloxy,
 C₂-C₇ alkoxy carbonyloxy,
 C₇-C₁₅ aryloxy carbonyloxy,
 C₈-C₁₅ aralkylcarbonyloxy,
 C₇-C₁₅ arylcarbonyloxy which may be substituted by nitro,
 five- or six-membered heteroaromatic acyloxy containing one oxygen or sulfur atom,
 five- or six-membered heteroaromatic acyloxy, containing a nitrogen or sulfur atom, which may be substituted
 by C₁-C₆ alkyl,
 five- or six-membered saturated heterocyclic carbonyloxy having at least one hetero atom selected from nitro-
 gen, oxygen, and sulfur atoms,
 C₁-C₆ alkylsulfonyloxy,
 C₂-C₇ alkylcarbamoyloxy,
 C₇-C₁₂ arylcarbamoyloxy,
 C₂-C₇ alkylcarbonylamino:
 R³ represents a hydrogen atom;
 R⁴ represents C₁-C₆ alkyl; and
 R⁵ represents a hydrogen atom.

26. A pharmaceutical composition comprising as an active ingredient the compound according to any one of claims 1 to 25.

27. The pharmaceutical composition according to claim 26, which is a therapeutic or prophylactic agent for progesterone-related diseases.

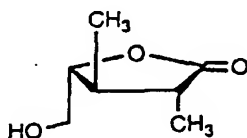
28. The pharmaceutical composition according to claim 26, which is an abortifacient, an oral contraceptive pill, an anticarcinostatic agent for breast cancer or ovarian cancer, a therapeutic agent for endometriosis, meningioma, or myeloma, or a therapeutic or prophylactic agent for osteoporosis or climacteric disturbance.

29. A method for treating or preventing progesterone-related diseases, comprising administering the compound according to any one of claims 1 to 25 to a mammal including a human being.

30. A method for treating or preventing abortion, contraception, breast or ovarian cancer, endometriosis, meningioma, myeloma, osteoporosis, or climacteric disturbance, comprising administering the compound according to any one of claims 1 to 25 to a mammal including a human being.

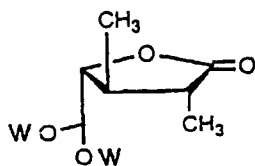
31. A process for producing a compound represented by the formula (I) according to claim 1, wherein R¹ and R² represent a hydroxyl group, R³ represents a hydrogen atom, R⁴ represents a hydrogen atom, optionally substituted C₁-C₁₀ alkyl, or C₂-C₁₀ alkenyl and R⁵ represents a hydrogen atom, said process comprising the steps of:

(a) oxidizing the following compound (11):



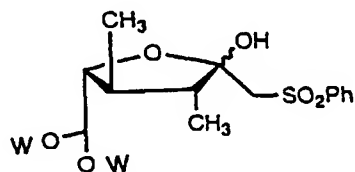
(1 1)

and then conducting acetal protection;
 (b) reacting the resultant compound (12):



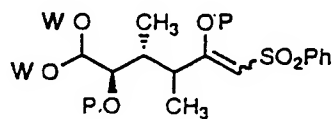
(1 2)

wherein W is a protective group of an acetal group, with benzenesulfonylmethyl in the presence of a base;
(c) protecting the resultant compound (13):



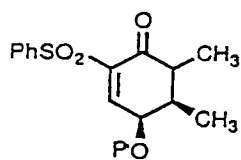
(1 3)

with a hydroxyl group and then conducting a ring-opening reaction in the presence of a base;
(d) subjecting the resultant compound (14):



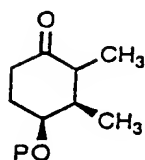
(1 4)

to a ring-closing reaction with a Lewis acid;
(e) reducing the resultant compound (15):



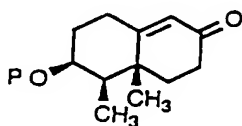
(1 5)

(f) subjecting the resultant compound (16):



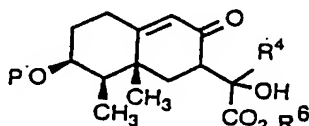
(1 6)

and 3-trimethylsilyl-3-buten-2-one to Michael addition and cyclocondensation in the presence of a base;
(g) condensing the resultant compound (17):



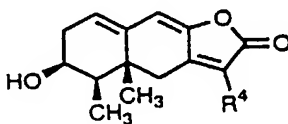
(1 7)

with α -keto ester by aldol condensation in the presence of a base and optionally a catalytic amount of zinc chloride;
(h) heating the resultant compound (18):



(1 8)

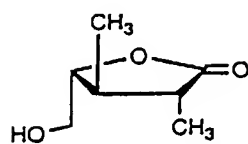
wherein R^4 is as defined above in connection with the formula (1) and R^6 is as defined above, under reflux in the presence of an acid catalyst;
(i) oxidizing the resultant compound (19):



(1 9)

32. Use of a compound represented by the following compound for the production of the compound according to any one of claims 1 to 25:

EP 0 885 893 A1



5

10

15

20

25

30

35

40

45

50

55

FIG. 1

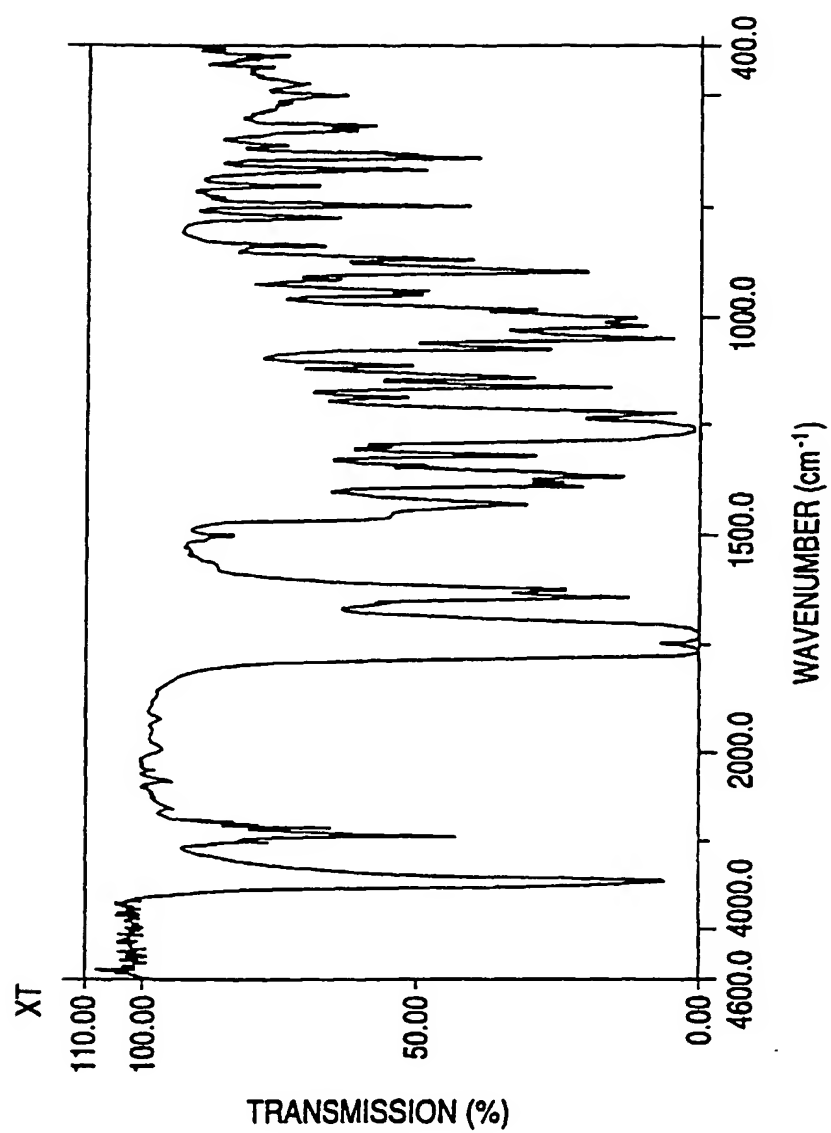


FIG. 2

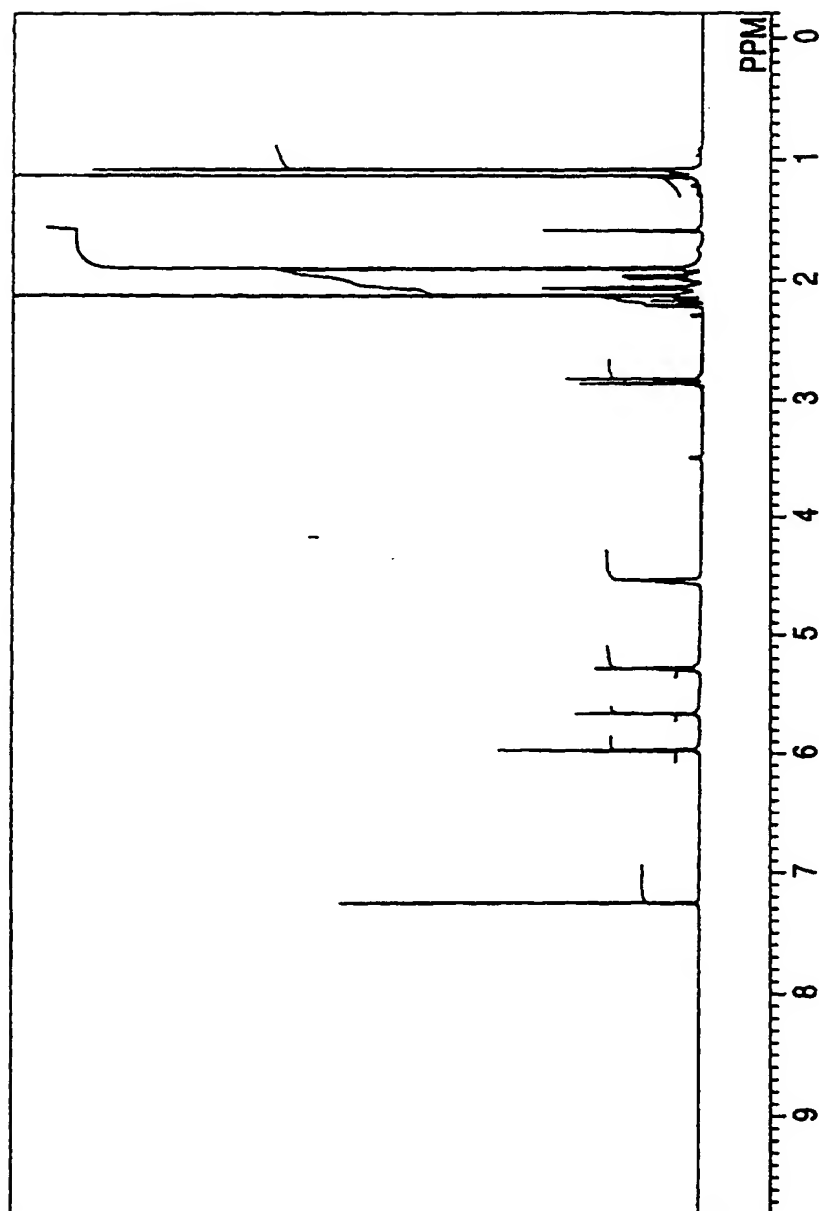


FIG. 3

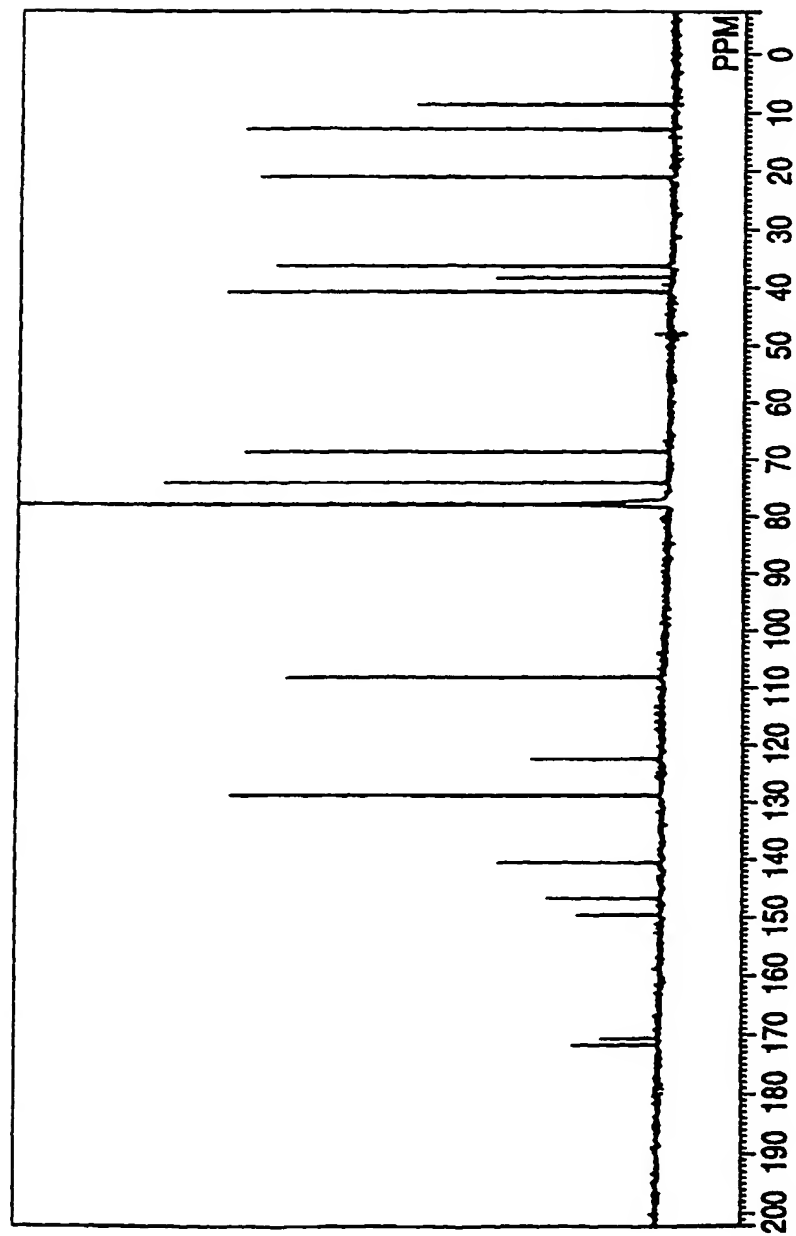


FIG. 4

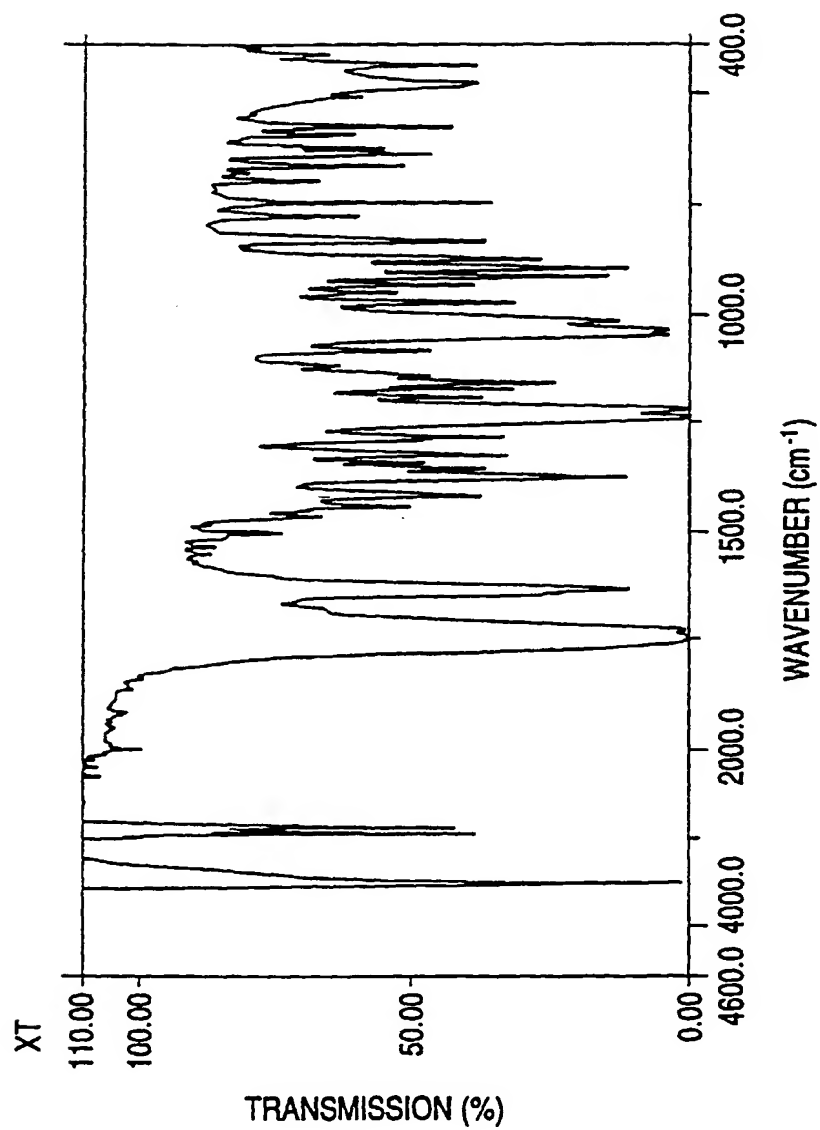


FIG. 5

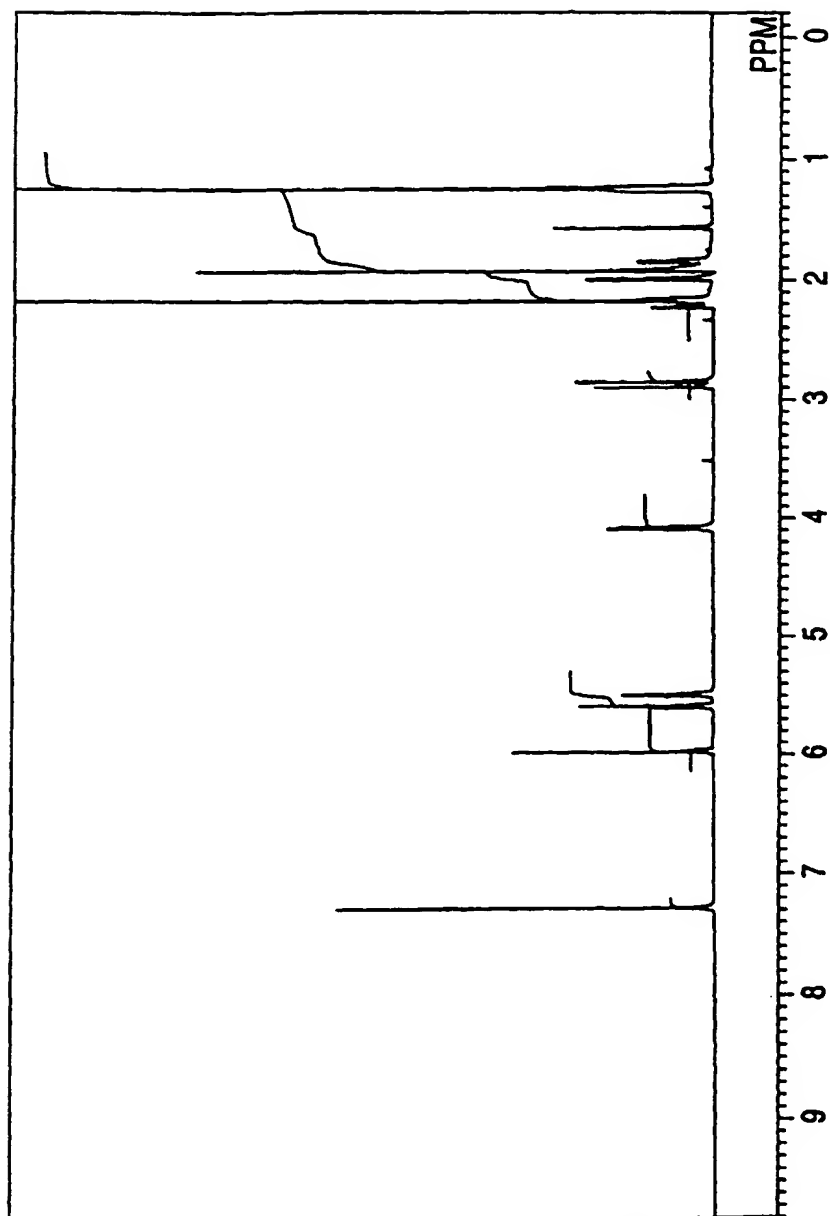


FIG. 6

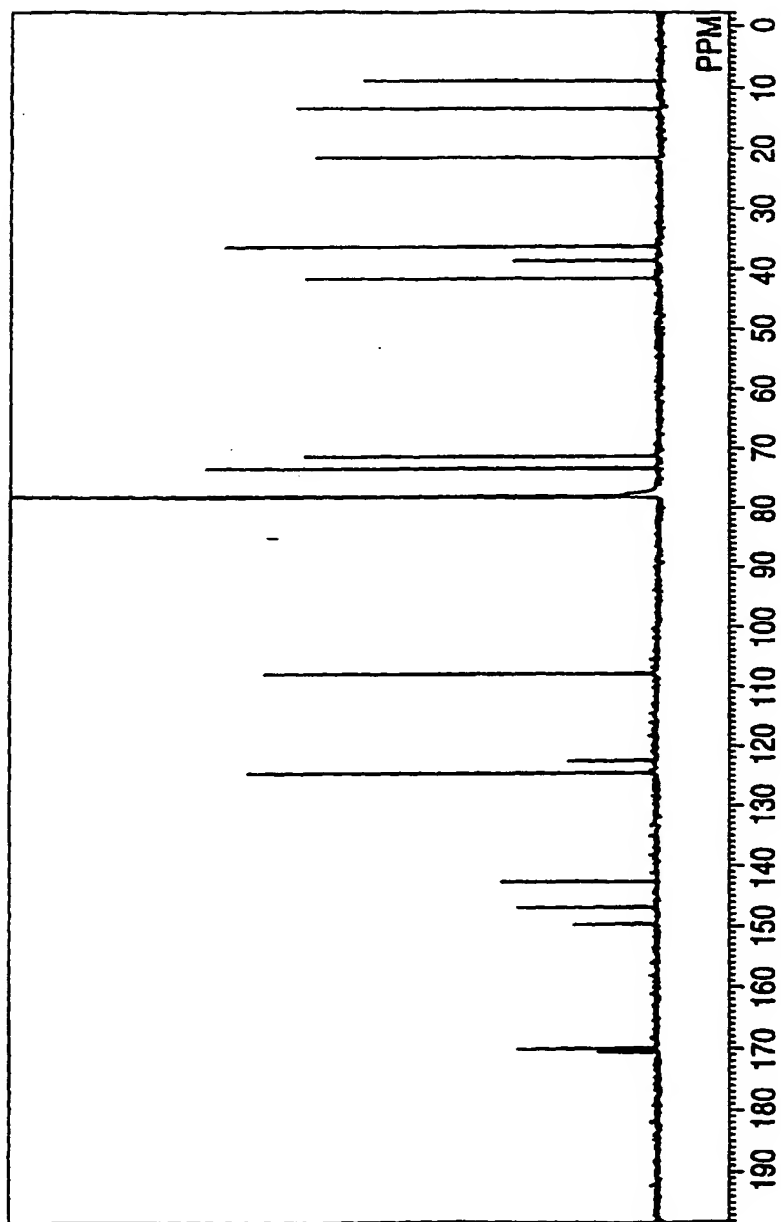


FIG. 7

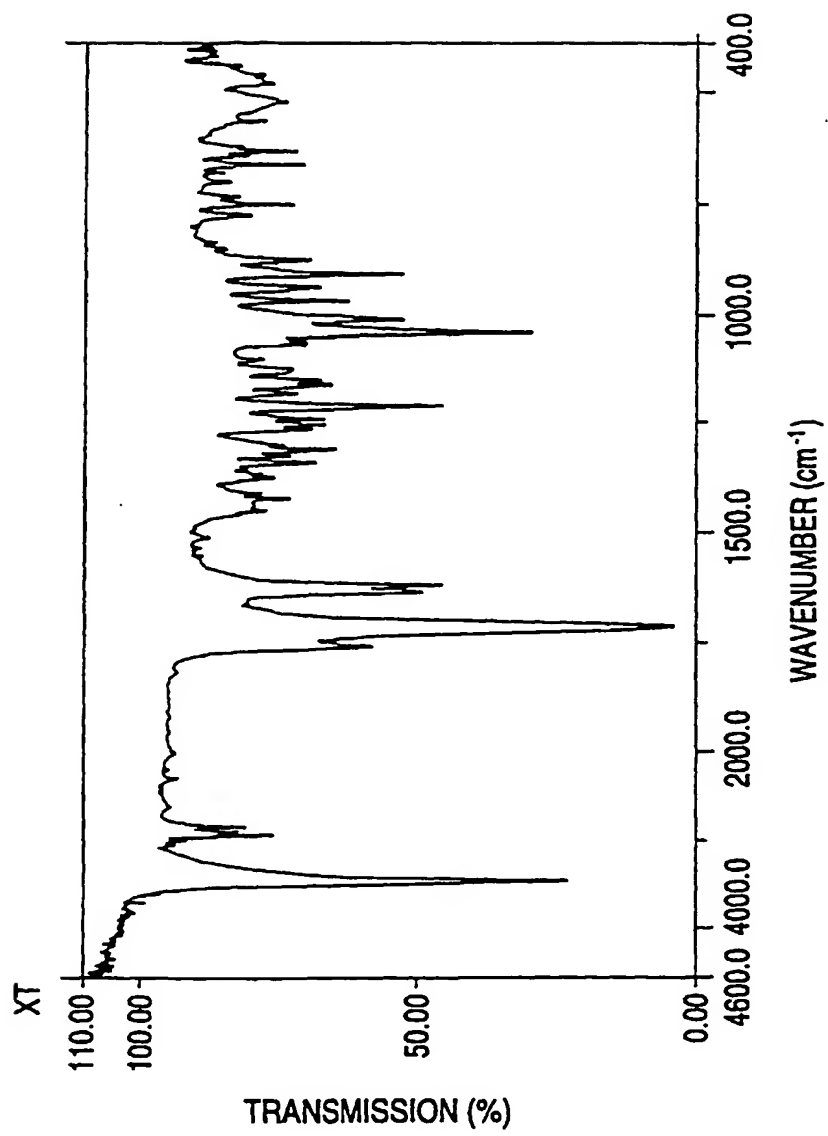


FIG. 8

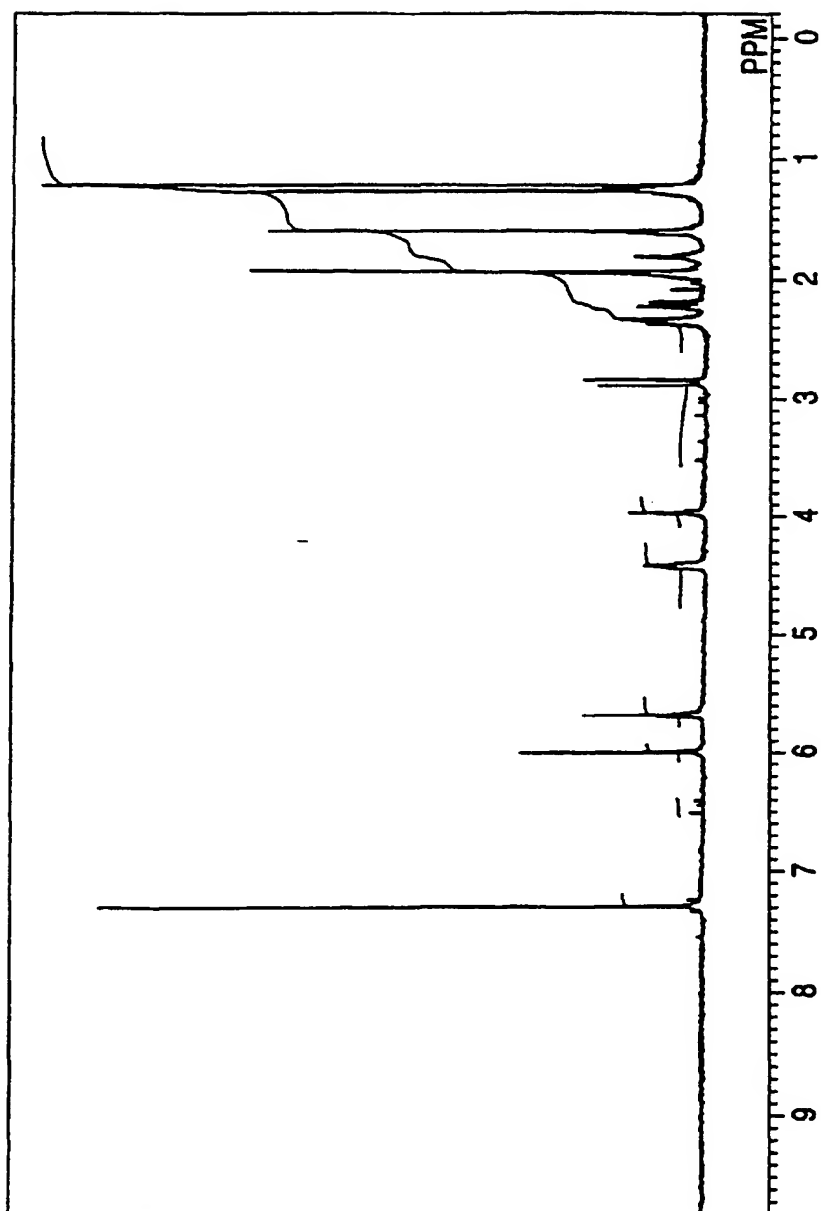
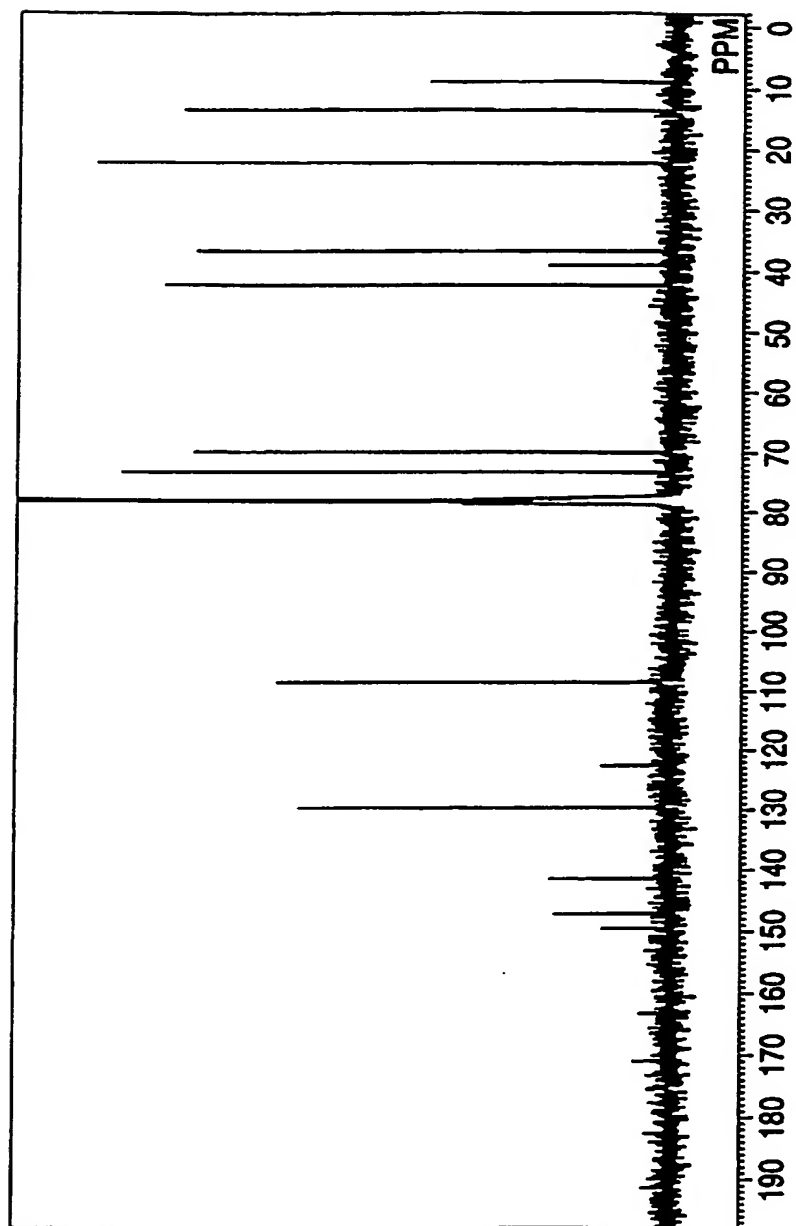


FIG. 9



EP 0 885 893 A1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP97/00451

A. CLASSIFICATION OF SUBJECT MATTER		
Int. C1 ⁶ C07D307/92, A61K31/365, C07D307/33		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
Int. C1 ⁶ C07D307/92, A61K31/34, 365, C07D307/33		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	Tetrahedron letters, Vol. 38, (No. 8), p. 1439-42, 1997; February 24, 1997 (24. 02. 97)	1 - 32
E	EP, 722940, A1 (Meiji Seika Kaisha Ltd.), July 24, 1996 (24. 07. 96) & JP, 8-253467, A	1 - 31
A	Tetrahedron, Vol. 26 (No. 23), p. 5387-5393 (1970)	1 - 32
A	Phytochemistry, Vol. 28 (No. 4), p. 1149-1153 (1989)	1 - 32
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search May 19, 1997 (19. 05. 97)		Date of mailing of the international search report May 27, 1997 (27. 05. 97)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)